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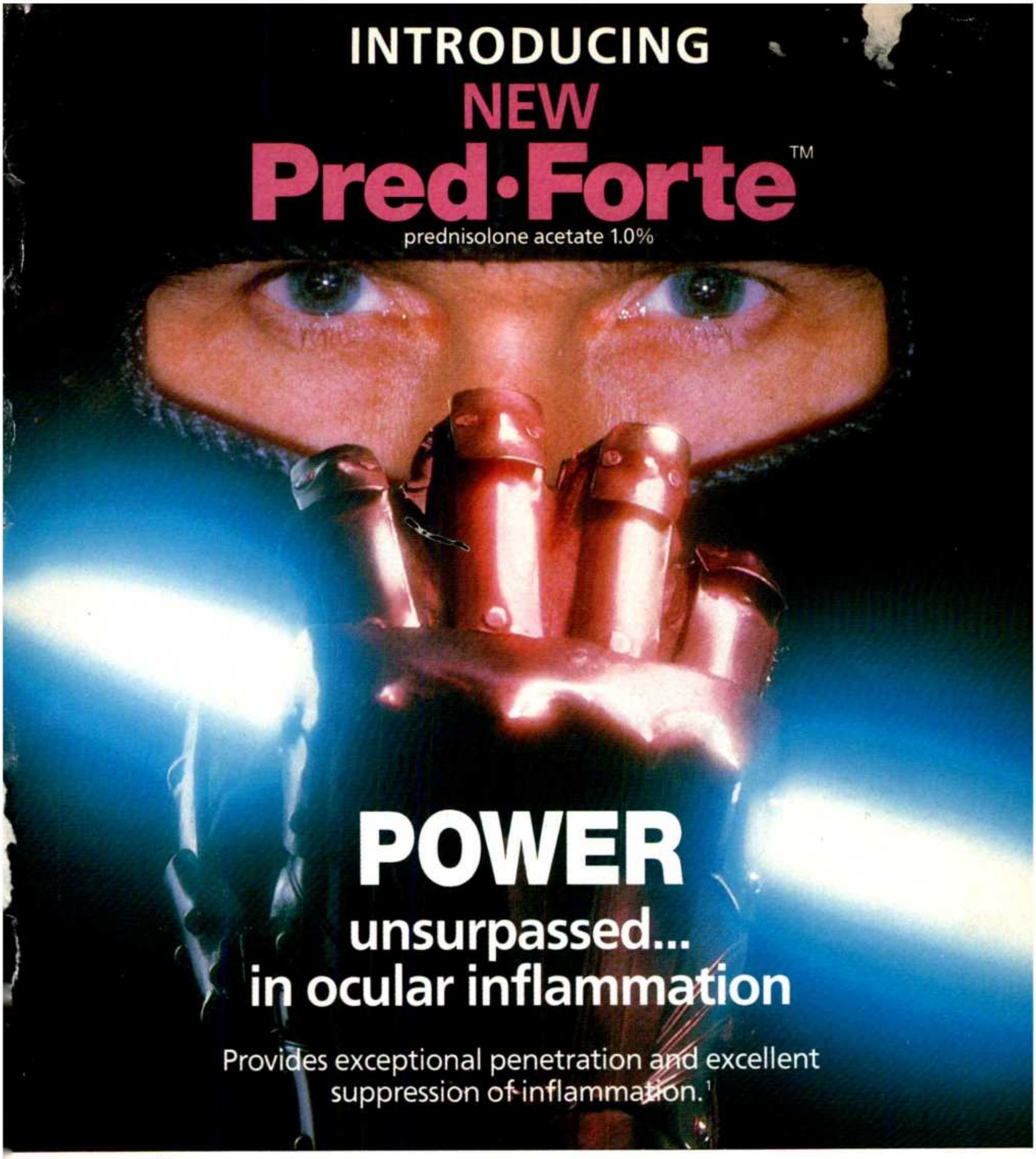
P 25,381



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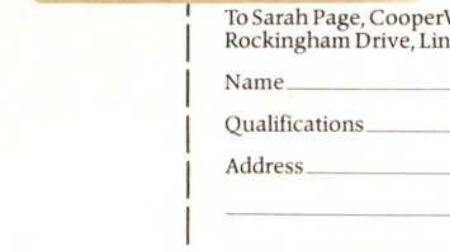

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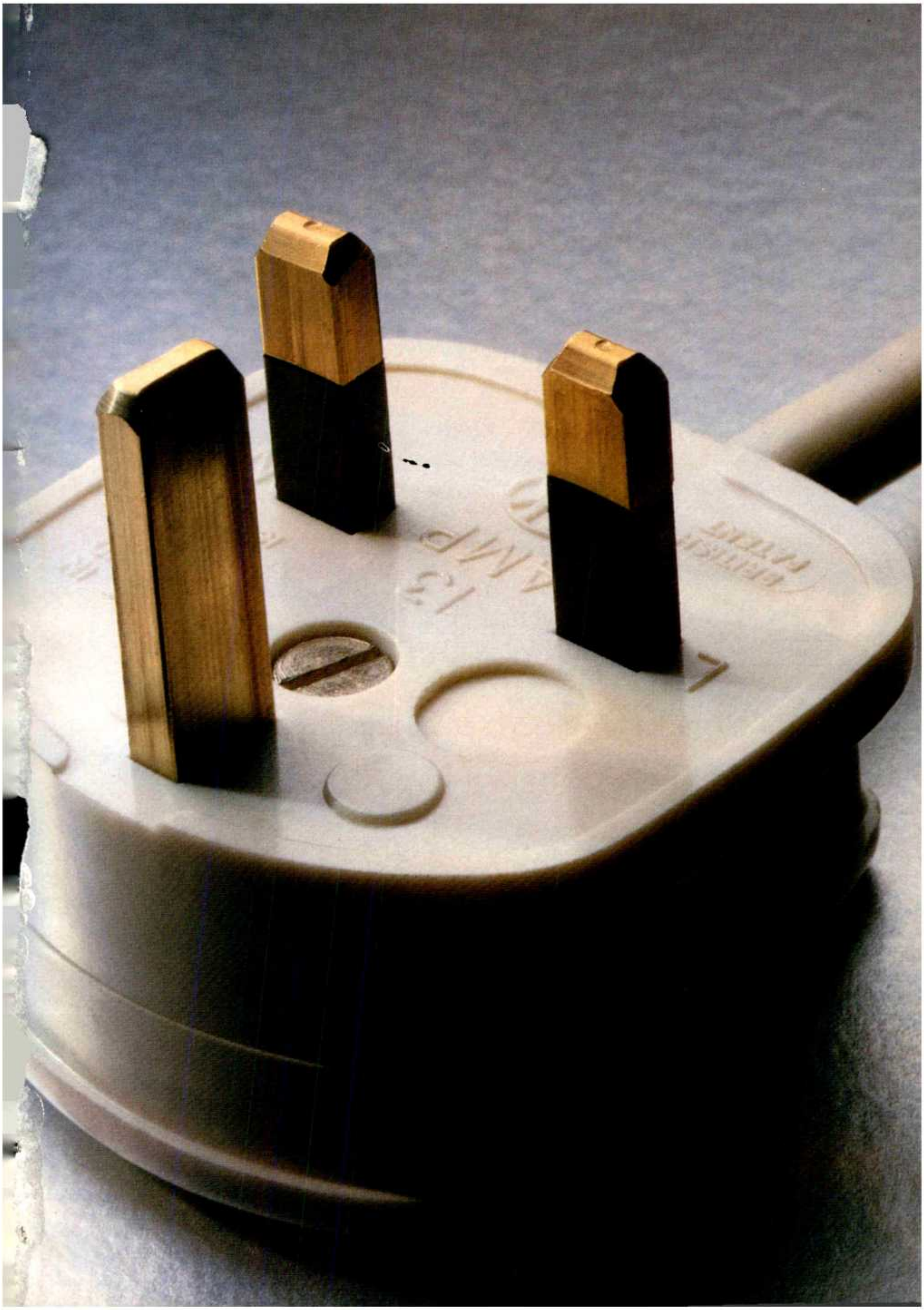
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British Journal of Ophthalmology, 1988, **72**, 481–484

Changing patterns of early complications in cataract surgery with new techniques: a surgical audit

J F ACHESON, J D McHUGH, AND M G FALCON

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SUMMARY We have undertaken a retrospective review of samples of case records from patients undergoing cataract surgery at St Thomas's Hospital over the years of the introduction of new extracapsular techniques and the widespread use of intraocular lens implants. We found no significant change in the proportion of patients achieving a corrected visual acuity of better than or equal to 6/12 three months after surgery. However, the pattern of complications was found to have changed in three respects. Firstly, there was a fall in the frequency of raised intraocular pressure requiring treatment associated with the abandonment of intracapsular surgery and the use of chymotrypsin. Secondly, a considerable number of patients who had had extracapsular extractions suffered from visually disabling posterior capsular thickening (13%). Thirdly, there was a downward trend in the rates of vitreous loss and of reduced vision at three months due to vitreous haemorrhage, vitritis, and retinal detachment in the patients undergoing extracapsular cataract surgery.

The debate surrounding the recent reintroduction of extracapsular cataract surgery has centred on two principal issues They are, firstly, the apparently superior reliability of posterior chamber intraocular lens implants,[1 2] and, secondly, the probable reduction in the incidence of certain visually disabling postoperative complications, in particular corneal decompensation, retinal detachment, and cystoid macular oedema.[3 7]

The argument is complicated by the fact that corneal endothelial cell loss and cystoid macular oedema may depend as much on pseudophakia as on the extraction technique.[4] Furthermore in one recent study there was no significant difference in the visual results of a series of patients undergoing intracapsular surgery and anterior chamber lens implant in the first eye and extracapsular surgery and posterior chamber lens implant in the second, indicating that the issue has yet to be settled.[8]

One aspect that has received less attention, however, is the question of immediate and early complications as the various new techniques are explored. Residents at the Bascom Palmer Eye Institute have been shown to learn to avoid posterior capsular rupture and vitreous loss according to a learning curve,[9] and it might be expected this would be reflected in the overall early complication rates when, in addition to teaching residents, senior surgeons are themselves exploring new techniques.

In parallel with national and international trends the Eye Department at St Thomas's Hospital has seen an almost complete switchover from intracapsular to extracapsular extractions between 1979 and 1985. In 1979 380 out of 385 extractions were intracapsular but by 1985 the number had fallen to 19 out of 574. In an attempt to detect any change in ocular morbidity when tried and tested techniques are supplanted by unfamiliar ones we have conducted a retrospective survey of serious postoperative complication rates and delayed early visual rehabilitation during this period.

Cheng and colleagues from the Oxford Octet study[10] have recently reported the interim results of their unique prospective randomised trial comparing other variants of these techniques, and have devised a scoring system for use in the systematic evaluation of visual results and complications applicable to all surgical techniques.[11] Such methods are not applicable retrospectively, and it is emphasised that this study is more in the nature of an audit of surgical performance over a period of great change rather than a trial attempting to demonstrate the superiority of one technique over another.

Correspondence to M G Falcon, FRCS

Materials and methods

Fifty eyes undergoing intracapsular extraction (IC) in 1979 (group I) and 54 eyes undergoing IC extraction in 1983 (group II) were studied. Operations from two separate years were examined to assess more accurately a baseline complications rate for IC extraction. Fifty extracapsular extractions (EC) from both 1984 (group III) and 1985 (group IV) were studied for comparison, these being the first years when this method was used in the majority of cases at St Thomas's Hospital. For analysis of the data the second of each pair of eyes in patients undergoing bilateral extractions was excluded, leaving 39 eyes in group I, 50 in group II, 47 in group III, and 49 in group IV.

The hospital clinical records were randomly located by means of the hospital activity analysis (HAA) prepared for computerised returns to the auditor at the regional health authority.

Preoperative and postoperative complications and the visual acuities three months after surgery were noted in each of the groups. The best corrected visual acuities (VA) were divided into two groups: those attaining better than or equal to 6/12, and those falling to 6/18 or below. A note was made of the apparent cause of reduced vision at three months The age of the patient and the presence of pseudophakia and coincidental ocular and systemic pathology were also noted.

Results

The results are recorded in Tables 1–5.

Table 1 *Composition of patient groups*

Group		
I	Total number of eyes	=50
	Total number of patients*	=39
	IOLs (iris clip)	= 1
	Mean patient age	69·6 years
II	Total number of eyes	=54
	Total number of patients	=50
	IOLs (all iris clip)	= 3
	Mean patient age	70·6 years
III	Total number of eyes	=50
	Total number of patients	=47
	IOLs (1 iris clip, 29 posterior chamber)	=30
	Mean patient age	71·5 years
IV	Total number of eyes	=50
	Total number of patients	=49
	IOLs (all posterior chamber)	=31
	Mean patient age	74 6 years

*Where one patient in the sample has had bilateral extractions the second eye has been excluded

All 89 patients in groups I and II underwent a standard intracapsular procedure with a limbal section, α-chymotrypsin, cryoslide, and virgin silk sutures

Table 2 *Principal operative and early postoperative complications*

Group	*I (n=39)*	*II (n=50)*	*III (n=47)*	*IV (n=49)*
Vitreous loss	2 (5%)	3 (3%)	1 (2%)	1 (2%)
Capsular rupture/ unplanned EC extraction	4 (10%)	6 (12%)	—	—
Posterior capsular rupture	—	—	4 (8%)	4 (8%)
Raised intraocular pressure*	5 (13%)	11 (28%)	4 (8%)	0

*Raised intraocular pressure defined as pressure over 25 mmHg on at least one occasion, associated with corneal epithelial oedema and requiring the prescription of hypotensive agents during the first 96 hours after operation

Table 3 *Complications apparently causing reduced visual acuity at three months after surgery*

	Groups	
	I and II (n=89)	*III and IV (n=96)*
Corneal oedema	8 (9%)	6 (6%)
Cystoid macular oedema	3	4
Posterior capsular thickening	—	12
Lens/capsular remnants	1	—
Retinal detachment	2	0
Persistent hyphaema	2	0
Vitreous loss/haemorrhage/vitritis	5	2
Uncertain	2	2
Totals	23	26

Table 4 *Coincidental ocular pathology apparently contributing to diminished visual acuity three months after surgery*

Diabetic retinopathy/maculopathy	5
Previous anterior segment surgery	5
Senile macular degeneration	4
Corneal scars	3
Endothelial guttae/Fuchs's dystrophy	2
Chronic uveitis	1
Myopic retinal degeneration	1
Macular hole	1
Chronic glaucoma	1
Previous retinal detachment surgery	1
Total (all groups listed together)	24 (12 7%)

Table 5 *Visual acuity scores three months after surgery*

Group	*I*	*II*	*III*	*IV*	*Mean*
Subtracting paired eyes					
≤6/12	28 (71%)	36 (72%)	34 (72%)	37 (75%)	72·5%
≥6/18	11	14	13	12	
Total	39	50	47	49	
Subtracting coincidental ocular pathology					
≤6/12	28 (86%)	36 (87%)	34 (81%)	37 (84%)	84 5
	implants only		19 (76%)	25 (89%)	
≥6/18	6	6	8	6	
Total	34	42	42	43	

Discussion

The years 1979–85 saw the adoption at St Thomas's Hospital of extracapsular cataract surgery in place of a well established intracapsular technique. In place of a standard procedure a wide variety of methods were used: for example, corneal and limbal sections; nylon and silk sutures; various designs of suction/aspiration apparatus; viscoelastic agents and air to maintain the anterior chamber and protect the corneal endothelium; and above all in many cases a wide variety of designs and models of intraocular lenses

Consultant surgeons have tried out new methods, and residents have been exposed to all the permutations. Against this background it is interesting to note that in these samples the major surgical complication rate, especially for vitreous loss, has clearly fallen. The vitreous loss rates of 5% and 6% for groups I and II (Table 2), and of 2% for both groups III and IV indicate a downward trend that should be compared with the figures of 1% and 3% in two recent reviews.[12 13] The same trend is seen for the vision-reducing vitreoretinal complications three months after surgery (Table 3) of vitreous haemorrhage, vitritis, and retinal detachment.

A further difference in the extracapsular groups is the reduction in the rate of early postoperative rise in intraocular pressure. Kirsch[14] first proposed a relationship between the use of α-chymotrypsin in cataract surgery and the occurrence of a self-limited postoperative glaucoma, but in extracapsular surgery sodium hyaluronate is associated with the same phenomenon.[15 16] However, in these samples of 96 extracapsular extractions sodium hyaluronate was used in only 35 cases, and the effect of abandoning α-chymotrypsin appears to outweigh the effects of introducing hyaluronate.

The frequency of 13% (Table 3) of patients in groups III and IV whose poor visual acuity (less than or equal to 6/18 at three months) appeared to be due to posterior capsular thickening may be compared with the figure of 14·3% reported by Seward and Doran[17] after a longer mean follow-up period of 26 months. This appears to be by far the commonest visually disabling complication in the extracapsular groups and may be treated either by surgical or YAG laser capsulotomy. However, such secondary procedures are not without risks, with particular respect to cystoid macular oedema, raised intraocular pressure, and pupil block glaucoma.[18]

The rates of persistent corneal oedema at three months remained constant at 9% and 6% in the intracapsular and extracapsular groups, and the similarity of these figures may reflect the fact that corneal endothelial cell loss both during and after surgery continues to be a problem with all techniques.[13] However, we have the strong clinical impression that the figure is nowadays much less.

Three months after surgery (Table 5) 72·5% of our patients achieved a corrected visual acuity of better than or equal to 6/12. This improves to a figure of 84·5% when coincidental ocular pathology (Table 4) is taken into account. No significant difference appeared between the proportion of patients from the intracapsular and the extracapsular groups reaching this level of visual function. The first group (group IV) in which the majority received intraocular lenses did well, with 89% achieving better than or equal to 6/12 after allowance was made for coincidental ocular pathology. These figures are comparable to the rates of 89·5% and 84·7% reported by Jaffe[2] and Karp and Scheie.[19]

In this audit of the case records of patients undergoing cataract surgery over a period of rapid change we could detect no significant excess ocular morbidity associated with the introduction of extracapsular techniques with posterior chamber implants. However, the pattern of early complications appeared to have changed markedly, with a reduction in the rates of posterior segment complications and the new need for secondary laser capsulotomy.

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The Ciapryna coaxial cannula

R V PEARSON AND J D JAGGER

From the Western Ophthalmic Hospital, Marylebone Road, London NW1

SUMMARY We describe a high quality, reusable, coaxial irrigation aspiration cannula for cortical cleansing during cataract surgery. Its advantages are that it is cheap, resterilisable, atraumatic, and has a rapid inflow, low-pressure irrigation rate enabling faster and safer aspiration of soft lens matter.

Numerous instruments and instrumentation systems have been designed for aspirating soft lens matter in extracapsular cataract surgery. These are usually of two main types, manually operated or automated. The latter are substantially more expensive to purchase and maintain, whereas manually operated devices are simpler and cheaper, and may differ in being bimanual, one-handed,[1 2] disposable, reusable, adaptations of other commonly available cannulae[3] or specifically designed. At the Western Ophthalmic Hospital we have helped Mr Bob Ciapryna design a refined, inexpensive, resterilisable, coaxial cannula with advantages over current commercially available instruments.

Description

The Ciapryna coaxial cannula (Fig. 1) consists of three components: (1) A 21-gauge aspiration needle 47 mm long which is obtainable with either a 0·2 mm or 0·3 mm single port, 0·075 mm from its smoothly rounded tip. The needle is mounted on a standard lockable Luer hub with a smoothly waisted connection which fits securely into and is shrouded by (2) a screw fitting nylon end plug that is leak-free. This screws into (3) the cannula body, also with a lockable Luer hub for the attachment of the irrigation drip tubing. The outer 1·5 mm irrigation cannula has two large 1·0 mm aperture ports 1·0 mm from its tip, which is smoothly tapered to enable an atraumatic entry into the eye to be made. The overall length is 6·5 cm. Parts 1 and 3 are made of medical grade chrome plated brass. It is sterilised by either ethylene oxide or steam autoclaving.

We have performed over 100 cases before any leakage from the nylon end plug occurred. Separate parts are readily obtained from the manufacturer if required.

Method of use

The aspiration needle is connected to either a 2·0 ml or 5·0 ml disposable syringe, partially filled with balanced salt solution. The irrigating port is connected via drip tubing to the irrigating fluid, and the rate of flow is adjusted by raising or lowering the infusion reservoir. The cannula is inserted through the section with the port visible, and fluid may be injected through the aspiration needle to deepen the anterior chamber, facilitating an atraumatic entry of the smoothly contoured coaxial cannula into the eye. Cortical cleansing is performed in the usual manner.

Comparison with other instruments

This coaxial cannula was designed to be an improvement on currently available manual coaxial cannulae with regard to cost, performance, and quality of manufacture. Multiple surgery is more expensive with single-use disposable cannulae. The latter are often less smoothly finished, and some varieties are not contoured and may cause trauma during entry into the eye, particularly stripping of Descemet's membrane. Reusable coaxial cannulae were expensive in the past but are now becoming less so. They are generally well machined and atraumatic. Both disposable and reusable types of cannulae require high hydrostatic pressures to maintain a rapid inflow rate, with the consequence in some patients of intermittent corneal oedema or a sudden, and at times alarming, movement of the posterior capsule posteriorly. We compared the pressure-flow relation-

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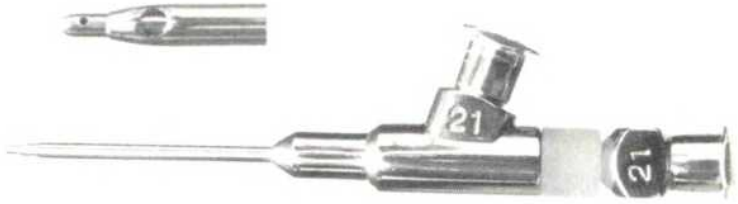

Fig. 1 *Assembled Ciapryna coaxial cannula.* Inset: *Contoured tip with irrigation and aspiration ports.*

ship of this cannula with that of other commonly available reusable and disposable cannulae. Table 1 shows that the flow rates through the Ciapryna cannula are greater at all hydrostatic pressures and that this cannula can also deliver a greater overall flow rate. There is thus less chance of high-pressure induced corneal oedema or fluctuating anterior chamber depth, with less risk of capsular or zonular rupture.

Table 1 *Relationship between flow rate (ml/min) and hydrostatic pressure, expressed as bag height in feet and mmHg for the cannulae investigated*

Reusable cannulae

Hydrostatic pressure=bag height in feet of water (mmHg)	*Cannula type*		
	*Simcoe**	*McIntyre†*	*Ciapryna*
	Flow rate (ml/min)		
1 (23·75)	4·61	1·17	8·59
2 (47·50)	10·34	3·24	24·09
3 (71·25)	15·60	5·83	38·05
4 (95·00)	16·44	7·63	46·49

Disposable cannulae

Hydrostatic pressure=bag height in feet of water (mmHg)	*Cannula type (Steriseal cannula model no.)*			
	1617	*1618*	*1622*	*1624*
	Flow rate (ml/min)			
1 (23·75)	4·84	4·84	4·70	2·17
2 (47·50)	8·45	9·18	9·68	4·25
3 (71·25)	13·33	13·10	14·28	13·33
4 (95·00)	15·58	15·58	16·90	18·18

*Simcoe double-barrelled irrigation/aspiration unit No. E4971, 23 gauge, 0·3 mm aspiration port. Stortz Instrument Co. (reusable). †Original McIntyre coaxial irrigation/aspiration cannula system No. E4395 3IEA. Stortz Instrument Co. (reusable). Metric conversion: 1 foot=30 cm.

Each cannula is hand made to a high standard, all components being flush fitting, all edges smoothed, and thus optimally atraumatic. The nylon end plug is recessed to accommodate the aspiration cannula hub, and this protects the fine bore of the inner aspiration needle from being bent or broken by inadvertent tangential traction forces during use. The smooth, atraumatic, waisted contour enables a watertight seal to be maintained between preplaced sutures, lessening leakage of irrigation fluid from the section with the advantage of substantially less irrigating fluid passing through the eye.

The cannula is designed to be highly cost effective, usually being cheaper than disposable units after use in 10 to 12 cases, and is placed towards the lower end of the price range of resterilisable cannulae. All ancillary equipment such as syringes and drip tubing is readily available and inexpensive. It has been used for over two years on over 500 patients by many surgeons, including those in training, both at the Western Ophthalmic Hospital and elsewhere.

The authors have no financial interest in this product. We are grateful to Shirley Pearson for secretarial assistance and Max Brown for photographic material.

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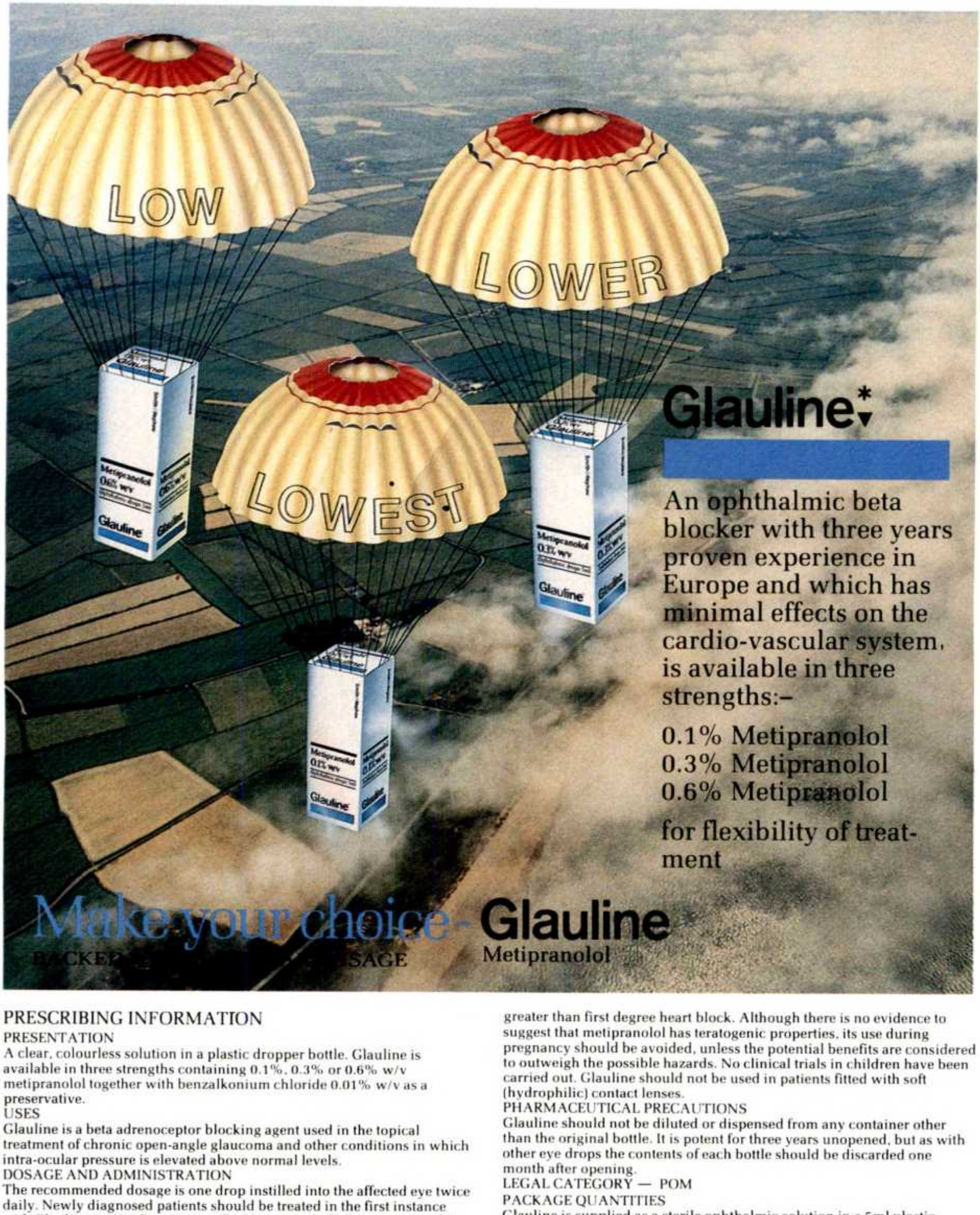

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The use of Glauline is not recommended in patients with obstructive airway disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Glauline should only be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block. Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards. No clinical trials in children have been carried out. Glauline should not be used in patients fitted with soft (hydrophilic) contact lenses.

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FURTHER INFORMATION

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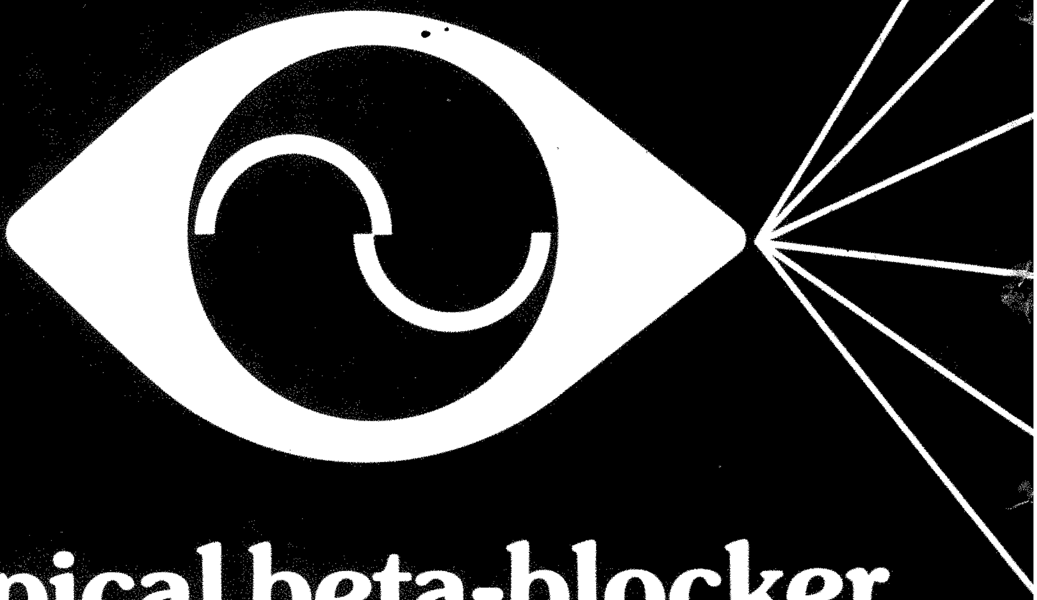

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British Journal of Ophthalmology, 1988, **72**, 487–493

Control of astigmatism in cataract surgery

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From the Nuffield Laboratory of Ophthalmology, Walton Street, Oxford OX2 6AW

SUMMARY A study is reported on cataract surgery, with intraocular lens implant, with measurement of the preoperative astigmatism and of the postoperative astigmatism over 28 weeks. Nine interrupted 10/0 nylon sutures are used to close a limbal section. Preoperative astigmatism is compensated for in the method of suturing by the placement of additional sutures. Postoperatively sutures are cut in line with the plus cylinder axis in eyes showing excessive astigmatism with the rule. Final postoperative astigmatism is controlled within 2·25 D cyl. 68% of cases lie within 1·0 D cyl with the rule to 1·0 D cyl against the rule. The average case in which sutures are not cut is one having 1.51 D cyl with the rule at one week postoperatively, declining to zero at approximately 12 weeks, and having a final value of 0·17 D cyl against the rule. No significant change in cylinder is seen after 10 weeks. The final postoperative astigmatism is only weakly correlated with the preoperative astigmatism, showing that the surgical method is effective. The spherical equivalent error is shown to shift in the direction of myopia in the postoperative period.

Astigmatism in the operated eye with an intraocular lens implant is most undersirable, since it reduces the effectiveness of the procedure. It is therefore worthwhile with these eyes to have an operating method that minimises astigmatism, even though it requires more time and attention by the surgeon.

Several factors responsible for surgically induced astigmatism have been identified. The most significant factor is in the tightness of the section closure.[1 2] A loosely closed section allows the cornea to flatten with reduced curvature in the vertical meridian (Fig. 1), causing astigmatism against the rule. If the section is closed tightly, it stretches the cornea vertically, increasing the curvature in the vertical meridian (Fig. 2) and causing astigmatism with the rule.[3] Other factors which have been defined are the preoperative astigmatism [1], the position,[4 5] length, and shape of the section, and the method of suturing,[2 6-11] the number of sutures,[12 13] sideways misalignment of section closure,[10] and the postoperative use of steroids.[14] In theory the further the section is made from the optical zone of the cornea[3] the less will inaccurate (over-loose or over-tight) suturing affect the astigmatism, and this is borne out in practice.[5 9] The longer the bite of each suture, the more will excessive tension in the suture affect the astigmatism.[15] The intraocular pressure (IOP), when raised, is a possible factor causing stretching of the section.

With the information available from the literature and from our previous experience it has become

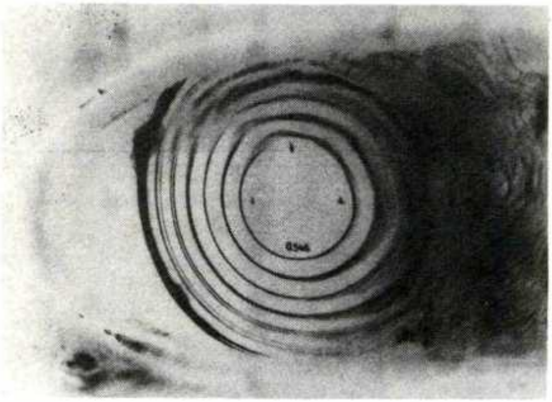
Fig. 1 *Keratograph of an eye postoperatively showing 3·50 D cyl against the rule due to a loosely closed section.*

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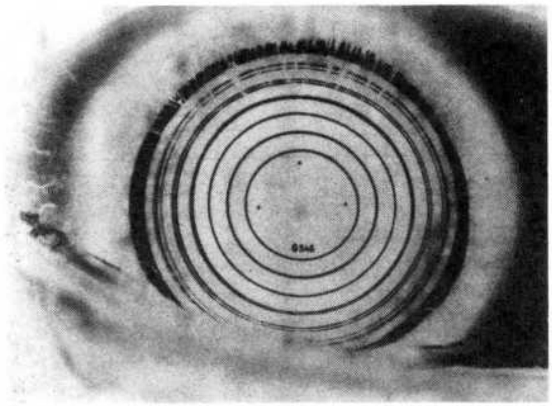

Fig. 2 *Keratograph of an eye postoperatively showing 1·75 D cyl with the rule. This is found to be the ideal initial postoperative result.*

possible to design an effective method of section closure. Our previous experience was with interrupted virgin silk sutures with a limbal section and continuous (bootlace) nylon suture with a corneal section. The silk sutures produced initially a with-the-rule astigmatism, which gradually reduced to produce, all too often, a significant against-the-rule astigmatism on completion of healing. The continuous nylon suture produced an initial with-the-rule astigmatism of a very variable amount. This showed less tendency to reduce with time, which has also been experienced by others.[2 16] However, there were a few cases in which the continuous suture appeared to lose tension at about three weeks postoperatively, allowing the sudden development of against-the-rule astigmatism. The use of a keratometer in the operating theatre,[14 17-23] prevents the cases of initial excessive with-the-rule astigmatism due to too tight a continuous suture, but it cannot guard against those cases that become slack subsequently, which would appear to be due to the interaction between the suture and the patient's tissue. We therefore concluded that interrupted sutures would be safer, since an individual suture becoming slack would not affect the entire section, and in addition these can be placed in a way to overcome the pre-existing astigmatism even when oblique.

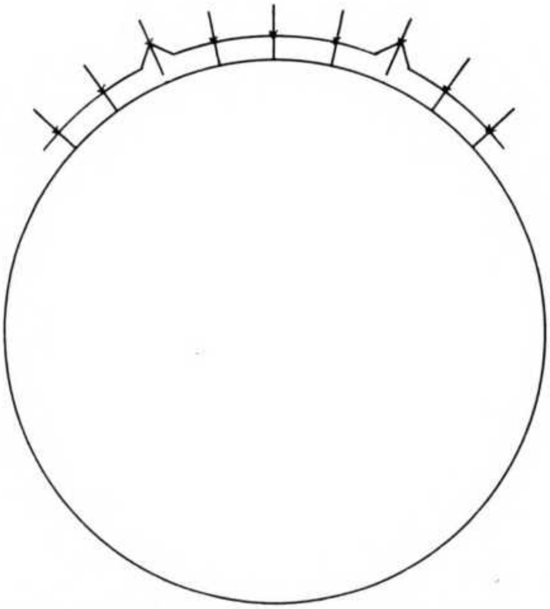

Fig. 3 *The limbal section with two 'cat's ear' notches to ensure accurate repositioning. Nine interrupted 10/0 nylon sutures are standard.*

Factors in postoperative astigmatism that we have not been able to take into account in the present study include tilt[24] and decentration of the lens implant.[25]

Materials and methods

SELECTION OF PATIENTS

One hundred consecutive eyes with cataract were included provided there was information on their previous refraction and the patients subsequently attended for follow-up to at least 22 weeks postoperatively. Ninety eyes received adequate follow-up and are reported on.

OPERATIVE METHOD

All eyes were operated on by the same technique. A limbus based conjunctival flap was followed by a 12 mm limbal section (Fig. 3) cut with a diamond and having two 'cat's ears' to half the corneoscleral depth. The 'cat's ears' ensure accurate repositioning of the section, and the first sutures are put in at these points. No preplaced sutures are used. The lens is extracted by the extracapsular method. After expression of the lens substance, one 10/0 nylon suture is inserted at the nasal 'cat's ear', prior to the aspiration of the remaining lens material and the insertion of a posterior chamber lens implant in the capsular sac. Sodium hyaluronate (Healonid) is used in all cases. The section is closed with interrupted 10/0 nylon. The needle is first passed into the section on the scleral side and then through the surface on the corneal side (Figs. 4A, B), so that the knot is formed in the depth of the section. The overall distance of needle passage through the tissue is kept short (1·4 mm). A surgical knot is followed by a third tie and the ends are cut short. The basic number of sutures is nine. If the

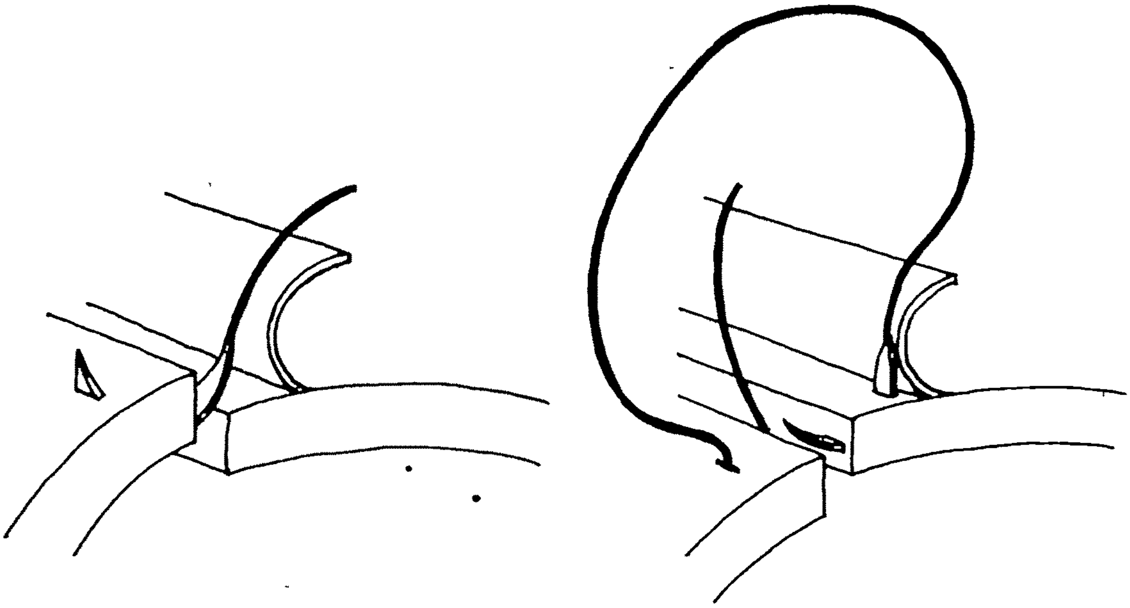

Fig. 4A Fig 4B

Fig. 4 A, B: *The method of corneoscleral suturing to form a buried knot with 10/0 nylon.*

patient had previously against-the-rue astigmatism, then additional sutures are added in line with the minus axis of the cylinder (Fig. 5). If the patient had previously with-the-rule astigmatism, the nine sutures are used and tied less firmly. Overtight suture tying by this method is uncommon, since the initial turn on the knot will slip before the second turn is added. Oblique astigmatism is corrected by additional sutures in line with the minus axis of the pre-existing cylindrical correction (Fig. 6). Acetazolamide 500 mg is given intravenously on completion of the operation.

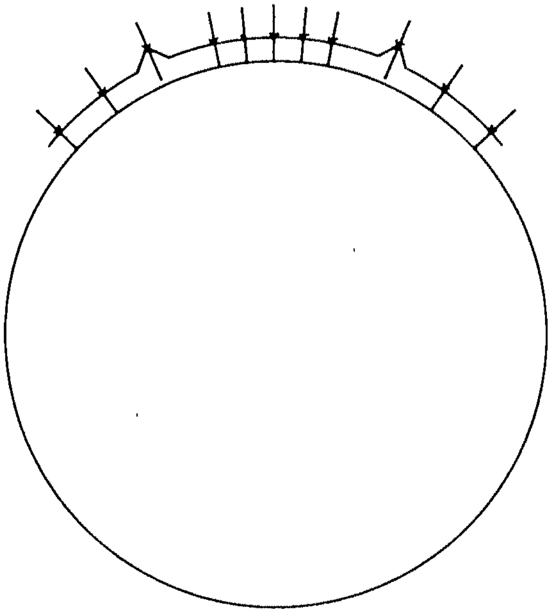

Fig 5 *Modified suturing to correct against-the-rule astigmatism by the insertion of additional sutures.*

POSTOPERATIVE MANAGEMENT

The patients received Maxitrol (neomycin, polymyxin B, dexamethasone) eye drops four times daily and Timoptol (timolol) eye drops 0·5% twice daily from the first postoperative day. The patients were seen at one week and two weeks postoperatively and then more variably, depending on individual needs at three, four, and six weeks, and then at longer intervals up to 22 weeks or longer. The patients were refracted and the applanation tension taken at each visit.

It was usual to find a with-the-rule astigmatism initially, which then declined. In patients showing a large initial with-the-rule astigmatic error of +3·0 D cyl or more, suture cutting was performed at one or two weeks postoperatively. When there was a persisting with-the-rule astigmatism of 2·25 D cyl or more at three weeks, suture cutting was initiated or further sutures cut in eyes that had already had sutures cut (Fig. 7). The procedure was continued up to six weeks, and in one case sutures were cut at 10 weeks.

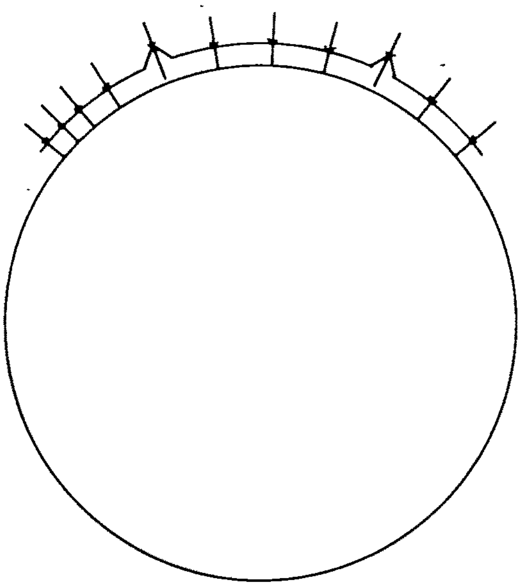

Fig. 6 *Modified suturing to correct oblique astigmatism In this case additional sutures are inserted to correct a pre-existing minus cylindrical correction at 150°*

Individual sutures were cut at the slit-lamp microscope, the first suture cut being that in line with the plus cylinder axis. These patients then attended one week after suture cutting, when further sutures might be cut. The part of the suture that is cut is the most corneal limit of it. The corneal part of the suture then retracts into the cornea, and the scleral part remains lying flat under the conjunctiva; the suture does not need removing. The suture cutting procedure was used in nine eyes and would have been used in two others, but the patients were unable to attend in the appropriate period.

The applanation tension was taken at each visit. All eyes showing tensions over 20 mmHg were continued on timolol eyedrops; otherwise the eyedrops given initially were stopped at one week Maxitrol eyedrops were given four times a day for one month, twice daily for the next month, and daily for the following month.

Results

Pre- and postoperative astigmatic errors are considered to be with the rule when the plus correcting cylinder lies between 46° and 135°, and against the rule when the plus correcting cylinder lies between 136° and 45°.

Of the 90 eyes completing this study the greatest final cylindrical refractive errors were 2·25 D with the rule and 2·25 against. 68% of the eyes had refractive errors within 1·00 D with the rule to 1·00 D against (Fig. 8). The distribution of final refractive errors was nearly even between with and against the rule (mean cylindrical error 0·17 D against the rule).

CASES NOT REQUIRING SUTURE CUTTING

Most of the patients had assessments at weeks 1, 3, 6, 10, and 28. Some patients' visits did not conform to these precise times—for example, a patient may have been seen at week 8 or 12. In such cases, in order to facilitate statistical analysis, linear interpolation was

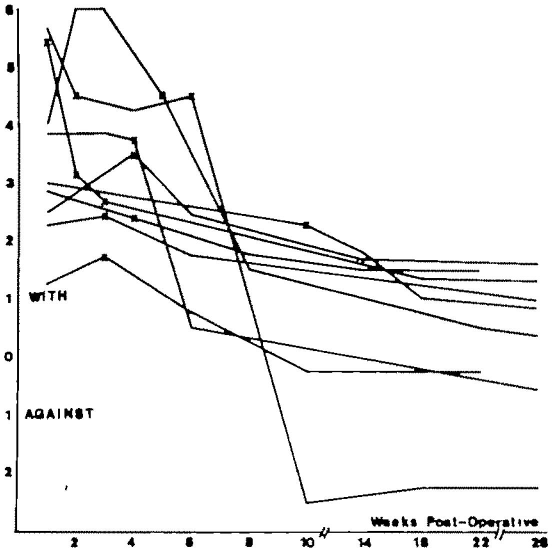

Fig 7 *Change in astigmatism in individual cases in which sutures cut. X marks the point in time when sutures cut.*

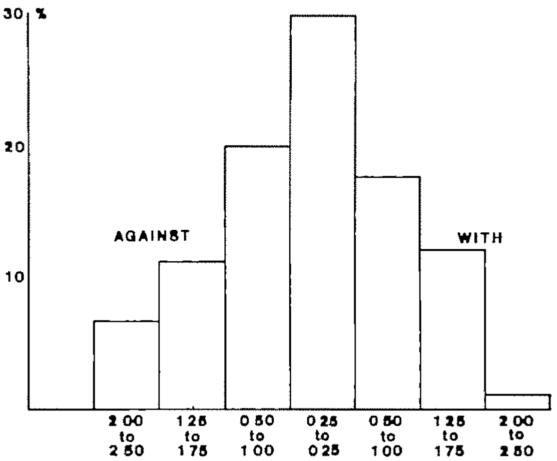

Fig. 8 *Percentage distribution of final refractive errors (all cases).*

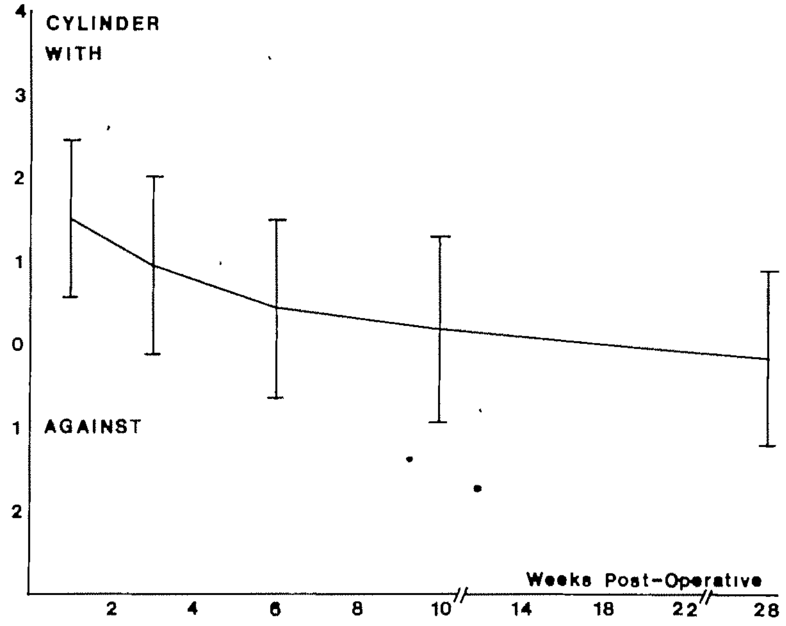

Fig 9 *Change in astigmatism with time in cases in which sutures not cut*

used to derive the expected refractive values at the required times as indicated above

Astigmatism with the rule was found to decrease from an initial mean of 1·51 D at week 1 to a mean of 0·18 D at week 10. This trend, illustrated in Fig. 9, was highly statistically significant; one-way analysis of variance yielded p=0·003. From the 10th to the 28th weeks there was a further slight reduction in with-the-rule astigmatism to a final mean of 0·17 D against the rule—that is, just crossing the point of zero astigmatism. There was, however, no statistical difference between the astigmatism at week 10 and that at week 28 (paired *t* tests, p=0·67).

The postoperative IOP was correlated with neither the initial rate of astigmatic decline (correlation coefficient=0·097) nor with the total astigmatic change (correlation coefficient=0·152).

The preoperative astigmatic error correlated weakly with final postoperative astigmatic error (correlation coefficient=0·243). This is illustrated in Fig. 10. There was no signficant difference between preoperative and final postoperative astigmatic error (paired *t* tests, p=0·746). The mean preoperative error was 0·12 D against the rule and the mean final postoperative error was 0·17 D against the rule. The variability of the preoperative astigmatism, however, was slightly greater than the postoperative; the standard deviation preoperatively was 1·34 D while that postoperatively was 1·05 D. These findings demonstrate that the surgical method counteracted the preoperative astigmatism.

The spherical equivalent changed postoperatively in the direction of myopia. This trend was highly statistically significant when tested against the null hypothesis that there should be no net change in spherical equivalent ($p<10^{-5}$) This change is illustrated in Fig. 11. This finding contrasts with the fact that the negative cylindrical error at 180° was decreasing.

There was a weak correlation between the IOP and the change in spherical equivalent (correlation coefficient=0·243).

The average case was one having 1·51 D cyl with the rule at one week, declining to zero at approximately 12 weeks, and having a final value of 0·17 D cyl against the rule. An eye seen at one week needing a +1·75 D cyl at 90° should be regarded as the ideal immediate surgical result.

CASES IN WHICH SUTURES CUT

Nine cases with significant initial with-the-rule astigmatism were included in this group (Fig. 7). Individual sutures were cut in line with the plus cylinder axis as early as one week and as late as 10 weeks postoperatively. Suture cutting was repeated in two eyes. The results in the individual eyes are shown in Fig. 7. The effect was most marked when performed early. One patient appeared to show an enormous change from with-the-rule to against-the-rule, which has been exaggerated by the simplification in defining with and against the rule astigmatism. This patient's course was: Week 1: −3·50/+5·50

P, 25, 381

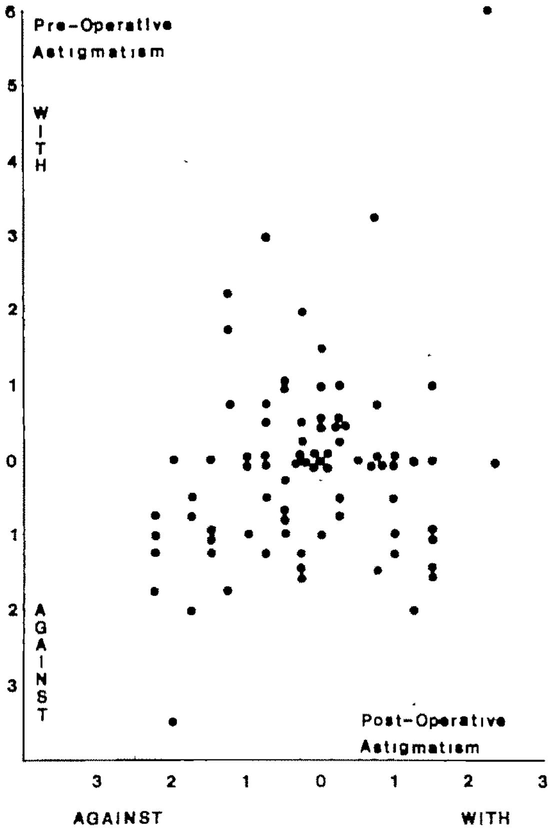

Fig. 10 *Correlation between preoperative astigmatic values and final postoperative astigmatic values (all cases).*

115°. Week 2: −4·00/+4·50 115°; suture cut at 11 o'clock. Week 4: −2·00/+4·25 140°. Week 6: −2·50/+4.50 145°; suture cut at 10.30 o'clock. Week 10: −1·00/+2·25 160°. Week 18: −1·00/+2·25 175°.

Discussion

Change in cylindrical correction is usually explained as a decrease in curvature of the vertical meridian postoperatively. If this were in fact the case, the spherical equivalent would be changing in the direction of hypermetropia. Our data show this not to be true, which means that another mechanism is operative. The most likely explanation is that the horizontal meridian is in fact steepening, and that this is the predominant effect, resulting in a myopic shift in the spherical equivalent. Other possible explanations include a forward movement of the intraocular lens implant, or an increase in the axial length of the eye, both of which seem unlikely. A study involving keratometry may shed light on the precise mechanism.

If astigmatism is to be minimised in the cataract section, greater effort is required on the part of the surgeon both peroperatively and postoperatively. Two methods of suturing emerge as superior: continuous suturing controlled by peroperative keratometry[14] or multiple limbal interrupted nylon sutures as used in the present study and by Bambery.[5] The peroperative keratometry requires extra manoeuvres in the operating theatre, including raising the intraocular pressure to a normal level.[14] The multiple interrupted nylon sutures with buried knots are

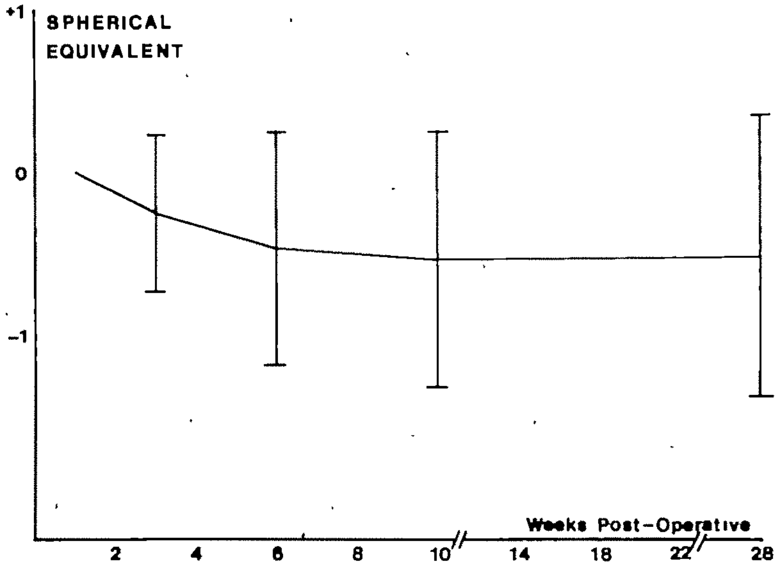

Fig 11 *Change in spherical equivalent error with time (uncut cases).*

tedious to insert. It is probable that each method adds a similar amount of time to the operation. The continuous suture with keratometer control can correct for the patient's preoperative astigmatism with or against the rule. Interrupted sutures, as used in the present method, can do this too, and they can also correct a preoperative oblique astigmatism. Interrupted nylon corneal sutures are also an effective method of section closure, but produced more, surgically induced astigmatism in comparison with the same sutures inserted limbally [4,5]

Postoperatively the surgeon has to be prepared to cut sutures.[1–3,5,14,16,23,26] The interrupted suture offers the surgeon the best opportunity for astigmatic control by suture cutting, since individual sutures can be cut in line with the patient's plus cylinder axis, and this does not weaken the entire section. Continuous sutures may be cut,[2,14] but if this is done too early the wound becomes slack and if it is done too late it is ineffective. The continuous suture may also be adjusted by easing it towards the tight meridian.[26] Our own experience suggests that the best time for cutting interrupted sutures is between one and six weeks, but others have found that later suture cutting is still effective,[5] and it is inadvisable to cut continuous sutures until seven weeks. The lack of correlation between the postoperative IOP and the rate of astigmatic decline shows that this study fails to demonstrate the relevance of the IOP. However, a raised IOP was deliberately guarded against by the medical treatment used in this study, and it remains possible that an uncontrolled IOP might affect the change in astigmatism.

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Cobalt plaque versus enucleation for uveal melanoma: comparison of survival rates

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SUMMARY Two hundred and twenty-three patients treated by cobalt plaque for uveal melanoma were compared with 416 patients treated by enucleation for uveal melanoma in terms of patient survival. The median follow-up time for the patients treated by cobalt plaque was 4·3 years. Kaplan-Meier survival curves were calculated up to five years following treatment based on time to tumour-related deaths. Cox's proportional hazards multivariate analysis was performed to determine which variables were related to melanoma-related deaths while controlling for age, size, and location of the tumours. Statistically significant predictive factors were location of tumour and largest tumour dimension. There was not a statistically significant difference in survival between patients treated by cobalt plaque and those treated by enucleation.

Many studies have explored prognostic factors and survival rates for patients with malignant melanoma of the choroid and ciliary body treated by enucleation.[1-4] A few studies have investigated similar factors with respect to treatment with cobalt-60 plaque therapy, but these have involved small numbers of patients and short follow-up times.[5-8] There has been, and continues to be, much discussion concerning the pros and cons of various types of treatment for malignant melanoma. The most basic issue in these debates would appear to be patient survival, yet no long-term study on a large patient population comparing treatment by enucleation with cobalt plaque, in terms of survival, exists. Comparison of prior studies is difficult: tumour dimensions have been variable, different methods of analysis have been used, patient numbers are small, and follow-up time short.[1-8] This study compares survival in terms of melanoma-related deaths between cobalt-60 plaque-treated patients (with long-term follow-up from multiple institutions in the United States and one in England) and patients treated by enucleation from the Massachusetts Eye and Ear Infirmary.

Material and methods

Three groups of patients with choroidal and ciliary body melanoma were compared for survival. Two hundred and sixty-seven patients, with a diagnosis of uveal melanoma from 1953 to 1973, treated by enucleation were identified from the records of the Eye Pathology Laboratory at the Massachusetts Eye and Ear Infirmary (MEEI). Thirty-two patients with histological extrascleral extension were excluded, leaving a total of 235 cases for group I. These subjects have been described elsewhere[4] and were part of a group of 267 cases with known survival status out of a total of 431 eligible patients.

Group II included 161 patients from MEEI with a diagnosis of choroidal and ciliary body melanoma whose eyes were enucleated from 1975 to 1981. From a total of 231 patients treated by enucleation during this period 20 were excluded because of extrascleral extension, and the survival status was unknown for another 50 patients.

Group III consisted of 223 patients with a diagnosis of uveal melanoma on the basis of clinical examination, indirect ophthalmoscopy, ultrasonography, and fluorescein angiography, treated by cobalt-60 plaque at several institutions: 142 cases from 1968 to 1984 identified from the records at the New York Hospital

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and Manhattan Eye, Ear and Throat Hospital; seven cases treated from 1975 to 1977 identified at North Shore University Hospital, New York; and 74 cases treated from 1954 to 1981 identified at St Bartholomew's Hospital, London. No patients had known extrascleral extension at the time of cobalt plaquing and all patients were included in the study.

Survival status, the date and cause of death, and metastatic disease status were determined up to 1 May 1983 in the enucleation groups and up to June 1984 in the cobalt plaque group by chart review, contact with patients, and their families, as well as contact with physicians. Survival status was recorded as alive without known metastases, alive with metastases, dead secondary to metastatic uveal melanoma, or dead from other causes. Metastases were confirmed by liver function abnormalities biopsy, or necropsy.

Tumour dimensions for the enucleation group were obtained from review of histopathological studies: the largest tumour diameter in millimetres in contact with the sclera, and elevation of the tumour in millimetres measured on the largest section available. For the cobalt plaque group the tumour dimensions were determined by visualisation by indirect ophthalmoscopy or by ultrasonographic measurements. The largest tumour dimension for each tumour, either diameter or height, was used in the analysis.

The location of the anterior margin of the tumour was coded as posterior to the equator or anterior to the equator, with or without involvement of the ciliary body.

Survival curves, based on deaths from uveal melanoma for the first five years after treatment for all three treatment groups, were calculated by the Kaplan-Meier technique.[10] Cox's proportional hazards multivariate analysis[11] was performed to determine which variables were independently associated with melanoma-related deaths. The four variables considered in the Cox model were: (1) treatment: cobalt-60 plaque, enucleation 1953–73, and enucleation 1975–81; (2) age: less than 40 years, 40–59 years, 60 years and older; (3) location of tumour: posterior to the equator or anterior to the equator; (4) largest tumour dimension (either diameter or height): small (up to 11 mm), medium (11–15 mm), or large (16 mm or greater)

The statistical analyses were performed through the computer facilities of the Department of Ophthalmology at the Massachusetts Eye and Ear Infirmary.

Results

The median age at enucleation of patients with uveal melanoma in group I (1953–73) was 58·5 years with a range of 18 to 95 years; in group II (1975–81), the median was 60 years with a range of 10 to 94 years. The age at cobalt plaque treatment for choroidal and ciliary body melanoma patients in group III ranged from 22 years to 84 years, with a median of 57·0 years. For two of the 223 cobalt plaque patients age at the time of treatment was not available.

Table 1 *Characteristics of tumours and patients according to treatment group*

Variable	*Cobalt plaque*		*Enucleation group I (1953–73)*		*Enucleation group II (1975–81)*	
Age (yr)	n	%	n	%	n	%
<40	28	12·6	18	7·7	17	10·6
40–49	35	15·7	49	20·8	16	9·9
50–59	61	27·4	62	26·4	34	21·1
60–69	51	22·9	69	29·4	49	30·4
70+	46	20·6	36	15·3	32	19·9
Unknown	2	0·9	1	0·4	13	8·1
Location						
Anterior	67	30·0	78	33·2	79	49·1
Posterior	154	69·1	138	58·7	80	49·7
Unknown	2	0·9	19	8·1	2	1·2
Largest dimension (mm)						
<11	152	68·2	113	48·1	68	42·2
11–15	67	30·0	87	37·0	71	44·1
16+	3	1·3	20	8·5	21	13·0
Unknown	1	0·4	15	6·4	1	0·6

Table 1 shows the distribution of characteristics according to treatment group.

The follow-up time in enucleation group I ranged from 100 days to 28 years, with a median of 9·3 years. In group II the follow-up time ranged from 90 days to 8·5 years, with a median of 3·3 years. In group III, the cobalt plaque group, the follow-up time ranged from 30 days to 30 years, with a median of 4·3 years.

Thirty-six of the 223 patients treated by cobalt plaque for uveal melanoma underwent subsequent enucleation. Of these 36 patients 4 died of metastatic melanoma and one of other causes Among the 188 patients treated only by cobalt plaque there were 18 deaths from metastatic disease and 11 from other causes. The analyses of patient survival comparing cobalt plaque treatment with enucleation were performed for all 223 cobalt plaque patients, including those 36 who underwent eventual enucleation. A further analysis was also made comparing the two enucleation groups, I and II, with the cobalt plaque group, excluding those with subsequent enucleation

SURVIVAL CURVES

Kaplan-Meier survival curves were calculated from tumour deaths for the first five years after treatment for all three treatment groups (Fig. 1); for only small

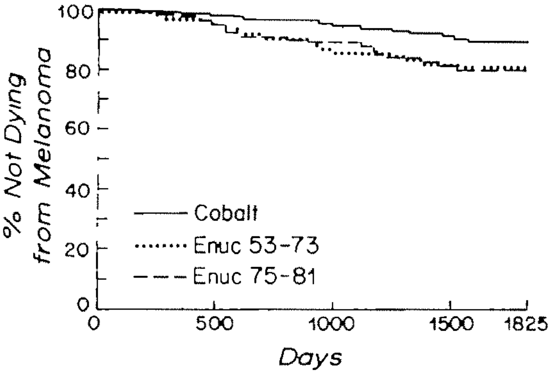

Fig 1 *Time to tumour death for all patients treated by cobalt plaque and enucleation.*

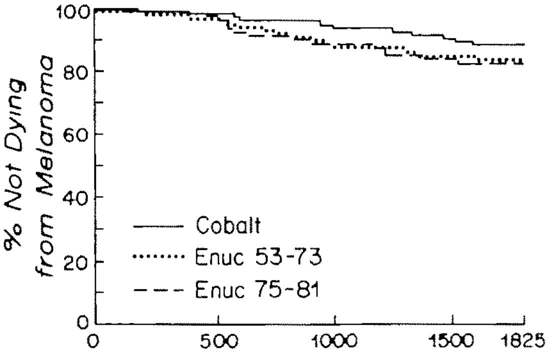

Fig. 2 *Time to tumour death for all patients with small and medium tumours treated by cobalt plaque and enucleation.*

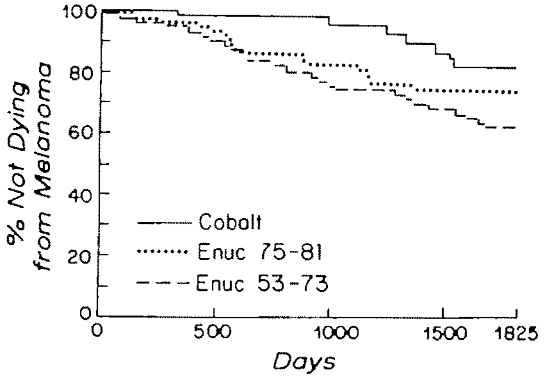

Fig. 3 *Time to tumour death for all patients with anterior tumours treated by cobalt plaque and enucleation*

and medium tumours (Fig. 2); and for anteriorly located tumours (Fig. 3). Cobalt plaque treated patients showed significantly better survival than either enucleation group (Fig. 1), and there was a statistically significant difference in survival for anterior tumours between cobalt treated patients and patients treated by enucleation from 1953 to 1973 (Fig 3). Other comparisons were not significantly different.

VARIABLES RELATED TO SURVIVAL

Cox's proportional hazards multivariate analysis, including the variables previously mentioned (treatment, age, location of tumour, largest tumour dimension), showed that anterior location and largest tumour dimensions (11–15 mm and 16 mm and greater) were significant prognostic factors for melanoma related deaths (Table 2). Patients with anterior tumours were twice as likely to die from melanoma in the first five years of follow-up as were patients with posterior tumours. In addition patients with tumours with 11–15 mm as the largest tumour dimension were 1·86 times as likely to die of tumour as patients with tumours 1–10 mm, and patients with tumours 16 mm or greater had a rate of melanoma death 3·3 times that of patients with a tumour 1–10 mm. When these and other factors previously mentioned were controlled, there was no significant difference in survival between the cobalt plaque treated patients and enucleation. Thirty-six of the 223 cobalt plaque treated patients eventually underwent enucleation. When these patients were excluded from the analyses, Kaplan-Meier curves showed no difference in survival between cobalt plaque patients and either enucleation group. This group was also analysed by means of the Cox model, which showed results similar to the analysis presented above, including all cobalt plaque patients.

Discussion

Previous studies of patient survival in choroidal and ciliary body melanoma have largely been directed

Table 2 *Results of Cox model analysis for deaths related to uveal melanoma*

Variable	*Comparison*	*Estimated rate ratio**	*95% Confidence interval*
Treatment	Enucleation group I vs cobalt	1·07	0·59–1·95
	Enucleation group 2 vs cobalt	0·77	0·39–1·51
Age	40–59 vs <40	0·84	0·34–2·05
	60+ vs <40	1·64	0·70–3·87
Location	Anterior vs posterior	2·07	1·27–3·37
Largest tumour dimension	11–15 vs <11	1·80	1·06–3·04
	16+ vs <11	3·31	1·67–6·55

*Estimated by the antilogarithm of the regression coefficients from proportional hazards model, with adjustment for all other variables presented toward one type of treatment. In terms of enucleation Flocks *et al.*[1] in 1955 had 73 out of 210 melanoma related deaths, McLean *et al*[2] in 1977 had 76 out of 217, Shammas and Blodi[3] in 1977 had 87 out of 293, and Seddon and Albert[4] in 1983 had 110 out of 274, with an average overall mortality of 34%

Studies of patient survival with cobalt plaque treatment include those of Stallard[5] in 1966 with six melanoma related deaths out of 100, MacFaul[6] in 1977 with 12 out of 107, Ellsworth[7] in 1978 with five out of 47, Migdal[8] in 1983 with five out of 90, and Brady and Shields[9] in 1984 with three out of 100, with an average overall mortality of 7%. Variable follow-up time makes meaningful comparison of these studies difficult.

A prior study comparing mortality data on a group of 100 patients treated by cobalt plaque with 100 patients treated by enucleation matched for age, sex, size of tumour, and follow-up from the Hahnemann-Wills Eye Hospital Group indicated for the cobalt plaque group a death rate of 0% for small, 2·4% for medium-sized, and 3·8% for large-sized melanomas. For their enucleation group death rates of 8·3%, 4·5%, and 22% respectively were found[9]

In contrast Gass[12] found a 50% probability of melanoma related death within five years after cobalt plaque in 21 patients, compared with 16% after enucleation in 27 patients.

Our study compares patient survival for cobalt plaque versus enucleation in a larger group of patients for a longer follow-up time for equally sized, aged, and located tumours by the same methods of analysis as have previously been described. Ocular survival, visual acuity, and radiation complications from cobalt plaquing, all important considerations in terms of type of treatment, were not included in this study but will be examined at a later date.

In conclusion, as in prior studies, overall patient survival for cobalt plaque is better than enucleation. As in prior studies of enucleation, survival for cobalt plaque is poorest with anterior tumours and is best with smallest tumours.

For equal sized tumours, at the same location with equal follow-up, survival with cobalt plaque is at least equal to survival with enucleation. Therefore, if enucleation for a uveal melanoma is planned, cobalt plaque should be considered the cure rate is the same, and obviously ocular survival, vision, and cosmesis are better.

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Intravitreal injection of fibroblasts: the pathological effects on the ocular tissues of the rabbit following an intravitreal injection of autologous skin fibroblasts

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SUMMARY The intravitreal injection of autologous cultured fibroblasts has been used by many groups to study proliferative vitreoretinopathy. Ninety-five New Zealand white rabbits were used to study the pathological effects on the ocular tissues following such an injection over various time periods up to six months. The ocular tissues were studied by light microscopy, electron microscopy, immunohistochemistry, and autoradiography. The cells which contributed to the inflammatory response (initially neutrophils, then later macrophages and lymphocytes) were found to gain entry into the vitreous via the pars plana, pars plicata, and the vessels associated with the optic nerve head. In the experimental eyes the detached retinae had a reduced ability to incorporate ^{3}H proline. Both epiretinal and subretinal membranes were found on the retinal surfaces. The majority of the glial cells within the membranes were identified as Müller cells. The retinal pigment epithelium beneath the detached retinae incorporated ^{3}H thymidine and detached into the subretinal space. Clear evidence was obtained of both epithelial cell migration through the retina and involvement within epiretinal membranes.

The intravitreal injection of tissue cultured autologous skin fibroblasts produces fibrous vitreal membranes which exert tractional forces leading to retinal detachment.[1-7] The fibroblast injection procedure has been used by several groups to study the antiproliferative activity of drugs which may have value in the treatment of proliferative vitreoretinopathy.[8-12] So far most of the morphological studies have centred on the organisation of the vitreal membranes,[2,4-7] which are principally the product of the injected cells.[5] Considerably less emphasis has been placed on the response of the retina, uvea, and other ocular tissues to the injection of cultured autologous fibroblasts into the vitreous

Sugita *et al*[2] were aware that the injection of autologous fibroblasts was associated with uveal inflammation. Although homologous fibroblast injection produces a biphasic response with plasma cells present in the second phase, autologous fibroblasts produce a non-immune reaction.[5] Tano *et al.*[8-11] described retinal neovascularisation and we observed retinal gliosis[5] in the autologous model. The autologous cultured fibroblast injection model is worthwhile only if the proliferative and reactive processes within the rabbit eye can be related to the human situation In the present study of autologous fibroblast injection into the rabbit vitreous the pathological changes within the retina and vitreous were examined by light microscopy, immunohistochemistry, autoradiography, and transmission and scanning electron microscopy. The principal aims of this investigation were to study in some detail the reactive changes in the retina with particular reference to the response of glia and retinal pigment epithelium. In addition an attempt was made to identify the main sites of entry of inflammatory cells into the vitreous.

Materials and methods

FIBROBLAST CULTURE AND INJECTION

Fibroblasts were cultured from skin biopsies which were aseptically removed from the rumps of New Zealand white rabbits.[5] After 2–3 weeks in culture the

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cells were removed by trypsinisation, centrifuged, and resuspended in phosphate-buffered saline (PBS) as previously described.[4] Cell viability within the suspension of fibroblasts was approximately 98% as estimated by the trypan blue exclusion method. Approximately 400 000 autologous fibroblasts in 0·2 ml sterile PBS were injected into the experimental (right) eye of each rabbit via the pars plana. Prior to the injection each experimental eye was softened by a paracentesis of the anterior chamber.

MORPHOLOGY (60 RABBITS)

The animals were killed at various times after the injection of fibroblasts, ranging from immediate to six months, by an overdose of sodium pentobarbitone. The eyes were enucleated and fixed by immersion into a cold 3% glutaraldehyde solution in cacodylate buffer. Prior to fixation a slit was made at the equator of the eye to enhance penetration of the fixative. After 24 hours the eyes were dissected, and the vitreal membranes were removed (these were used in other studies). Pieces of limbal tissue, iris, ciliary body up to the ora serrata, optic nerve head, and retina were then postfixed in a 1% osmium tetroxide solution and dehydrated through a graded series of alcohols. The injection site was not identified in any of our specimens. Tissue for transmission electron microscopy was embedded in either Araldite or Epon (see autoradiography section). Propylene oxide was used as the intermediate fluid. Semithin sections (approximately 1 µm) were cut on an ultramicrotome (Huxley) and stained with a 1% aqueous solution of toluidine blue. Ultrathin sections (70 nm) were cut on an automatic ultramicrotome (Ultracut E, Reichert-Jung) and stained with lead citrate and uranyl acetate. The tissues were viewed and photographed in a JEOL 100C transmission electron microscope. Specimens for scanning electron microscopy, after alcohol dehydration, were dried further in a critical point drier (Polaron), and then the specimens were sputter coated with gold (Polaron). The tissues were examined and photographed in a Hitachi S 520 scanning electron microscope. Any remaining tissue from the eyes was processed for routine paraffin wax histology. The wax sections were stained with haematoxylin and eosin.

IMMUNOHISTOCHEMISTRY (33 RABBITS)

After the rabbits were killed the eyes were enucleated, fixed in 10% formal saline, and processed for paraffin wax embedding. Sections (5–8 µm) were cut and mounted on glass microscope slides precoated with a solution of 0·1% poly L-lysine.

Three of the rabbits had not been injected with fibroblasts and were used as controls for the staining of normal tissues for the presence of actin and prekeratin.

Actin (13 rabbits)

The tissues were pretreated with hydrogen peroxide to remove any endogenous peroxidase and normal swine serum to prevent non-specific staining from the link immunoglobulin. Serum containing antiactin antibodies was raised in our laboratory.[7] The primary antibody was diluted 1:40 with trometamol (Tris) buffered saline (TBS). The pig antirabbit immunoglobulin link and the rabbit peroxidase-antiperoxidase complex were diluted 1:50 with TBS. The substrate for the peroxidase reaction was a 0·05% solution of 3·3-diamino benzidine tetrahydrochloride (DAB) plus 1% hydrogen peroxide in 0·2 M trometamol solution Appropriate controls were conducted which have been described previously.[7]

Prekeratin (23 rabbits)

A standard immunoperoxidase technique was used to stain the wax sections for the presence of prekeratin. The primary antibody was guinea-pig antiprekeratin to bovine hoof (Miles Scientific, Slough) and was diluted 1:30 with TBS. The peroxidase-labelled antiguinea-pig immunoglobulin was diluted 1:30 with TBS. The substrate for the peroxidase reaction was DAB.

The positive staining of cultured corneal epithelium was used as a control for the presence of prekeratin.[13]

AUTORADIOGRAPHY (23 RABBITS)

Thymidine

Twelve rabbits having received an intravitreal injection of fibroblasts for various time periods (2 days–10 weeks) were given a further ipsilateral intravitreal injection of 30 µCi (30 µl) of [methyl $-^3$H] thymidine (Amersham International PLC, Amersham) 24 hours prior to death. One rabbit received radiolabel only and served as a control.

Proline

Nine rabbits which had been injected with fibroblasts for various time periods (1–10 weeks) were given an injection of 30 µCi (30 µl) of L-[5 $-^3$H] proline (Amersham International PLC, Amersham), 24 hours prior to death. One rabbit which had the injection of proline without the earlier intravitreal fibroblast injection served as a control.

Tissue processing

Following death and enucleation the ocular tissues were processed and embedded in Epon as described

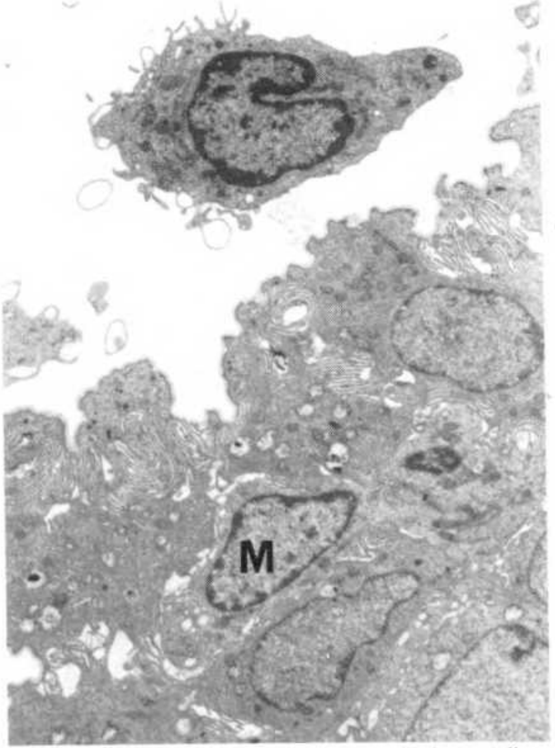

Fig. 1a *A transmission electron micrograph of a partially oblique section of epithelium from the posterior portion of the ciliary processes. Six days after the injection of fibroblasts a macrophage* (M) *is evident within the distended extracellular spaces of the epithelium. ×3825.*

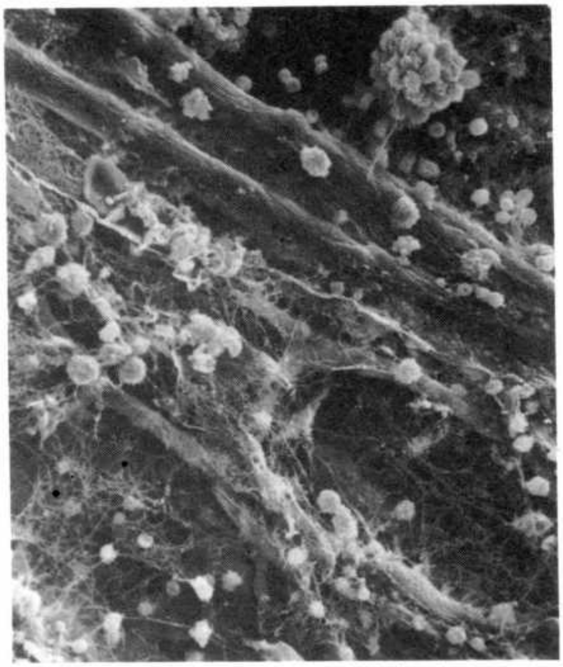

Fig. 1b *A scanning electron micrograph showing aggregates of inflammatory cells in close association with the vascular complex on the medullary rays three days after the intravitreal injection of fibroblasts. ×407.*

earlier. Semithin sections were processed for autoradiography as described by Hitchins and Grierson.[6] The autoradiographs were left in the dark at 4°C for an exposure time of six weeks for ^{3}H thymidine and 11–12 weeks for ^{3}H proline. The autoradiographs were then developed and stained with a 1% alcoholic solution of toluidine blue at room temperature. The sections were examined under a light microscope.

Results

INFLAMMATION

Inflammatory cells invaded the vitreal cavity during the first few days following the intravitreal injection of autologous fibroblasts and were associated with the vitreal proliferations which developed. The inflammatory cells gained entry to the vitreous by two key areas, via the epithelium of the pars plana and pars plicata (Fig. 1a) and the vascular complex associated with the medullary rays of the optic nerve head (Fig. 1b). During the acute stage of inflammation polymorphonuclear leucocytes were prominent throughout the uvea and vitreous. After one week the infiltrate consisted mainly of lymphocytes and macrophages. The mononuclear cells were present until the fourth week, after which they were seen infrequently. The meshwork of the anterior chamber appeared to remain free of inflammatory cells.

VASCULATURE ASSOCIATED WITH THE MEDULLARY RAYS

The incorporation of ^{3}H proline was more pronounced in the perivascular cells of the control tissue than at any stage following fibroblast injection (Fig. 2). Fibroblast injection resulted in the vessel basement membranes becoming multilayered, and swollen mitochondria in the endothelium were commonly seen.

INNER RETINAL SURFACE AND EPIRETINAL MEMBRANE FORMATION

Areas of retinal surface were noted by SEM to be denuded of cortical vitreal collagen one week after the fibroblast injection. After three weeks small bulges were seen protruding through the inner limiting lamina (ILL) into the vitreal cavity (Fig. 3a). Occasionally evidence of cell processes extending through the ILL on to the vitreal surface of the retina

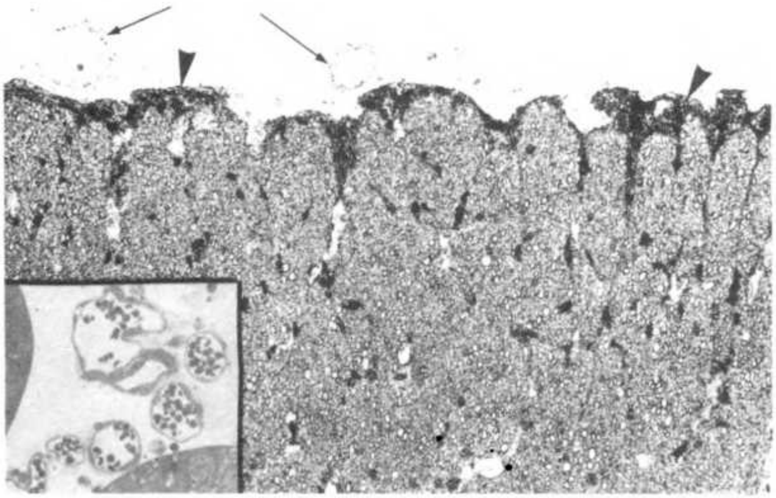

Fig. 2 *Autoradiograph showing the incorporation of ^{3}H proline within the control rabbit's optic nerve head. Label was seen particularly in the glia (arrowheads) and the perivascular cells (arrows). ×175. Insert: Autoradiograph four weeks after an intravitreal injection of fibroblasts the incorporation of ^{3}H proline had decreased substantially. ×175.*

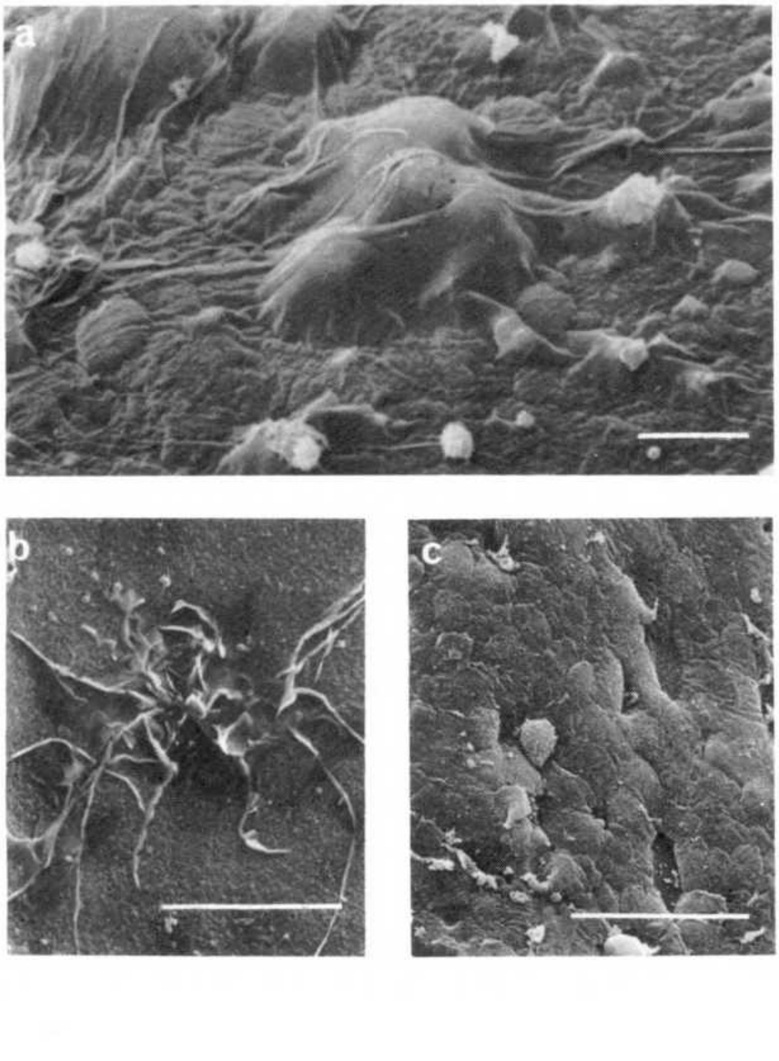

Fig. 3 a: *SEM showing bulges on the inner retinal surface three weeks after a fibroblast injection. ×700.* b: *SEM demonstrating a cell extending its processes through the inner limiting lamina only three days after the injection. ×2300.* c: *SEM of plate-like glia which had formed an epiretinal membrane 10 weeks after the injection of fibroblasts. ×460. Bar markers are* (a) *20 µm,* (b) *10 µm, and* (c) *50 µm.*

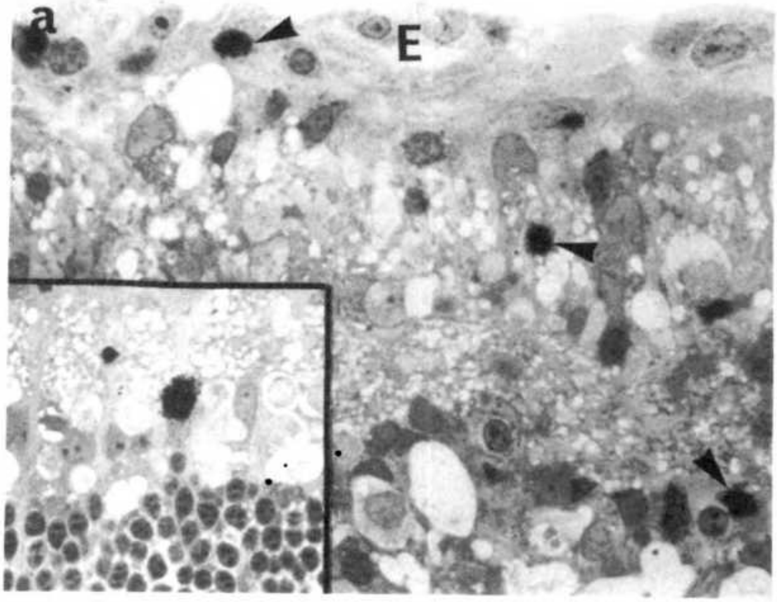

Fig. 4a *Autoradiograph showing the incorporation of ^{3}H thymidine within the rabbit's retina one week after a fibroblast injection. Clusters of grains (arrowheads) were seen within the nuclei of the cells of the epiretinal membrane* (E), *nerve fibre, ganglion cell, and inner nuclear layers.* ×*336.* Insert: *High power of grain cluster within the nucleus of a cell from the inner nuclear layer.* ×*480.*

was found as early as three day after the injection (Fig. 3b). At the 10-week stage cells were clearly visible on the retinal surface, and often these cells contributed to foci of monlayers or even multilayers of plate-like glial cells (Fig. 3c).

Incorporation of ^{3}H thymidine, as indicated by large clusters of silver grains, was not found within the nuclei of the retinal cells in the control tissue. However, one week after the injection of fibroblasts sporadic nuclear incorporation of ^{3}H thymidine was evident within the retina, particularly in the inner nuclear layer (Fig. 4a). Also at one week labelled nuclei were a feature of the newly developing epiretinal membranes (Fig. 4a). Labelled nuclei were

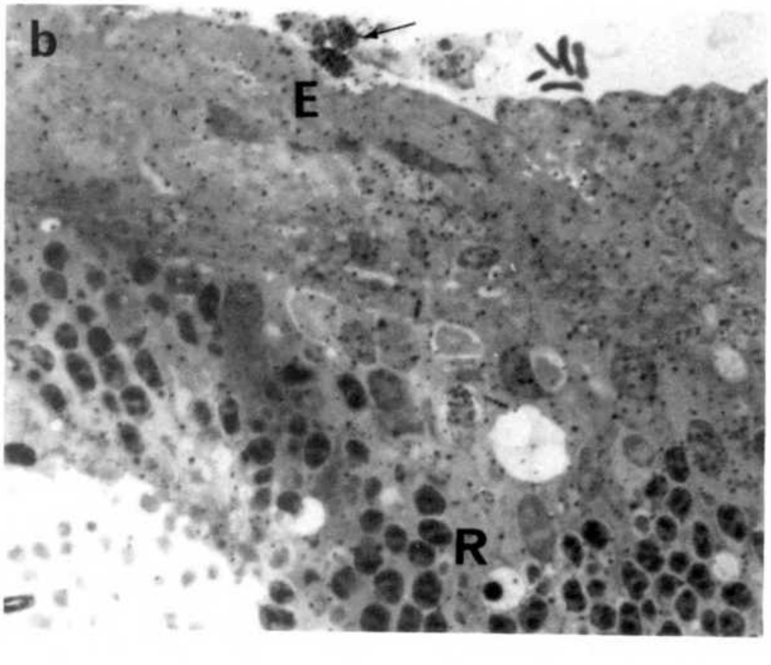

Fig. 4b *Autoradiograph showing the diffuse pattern and low level of ^{3}H proline incorporation within the degenerating retina* (R) *and overlying epiretinal membrane* (E) *two weeks after a fibroblast injection. Note two cells of the epiretinal membrane with high levels of incorporation (arrow).* ×*768.*

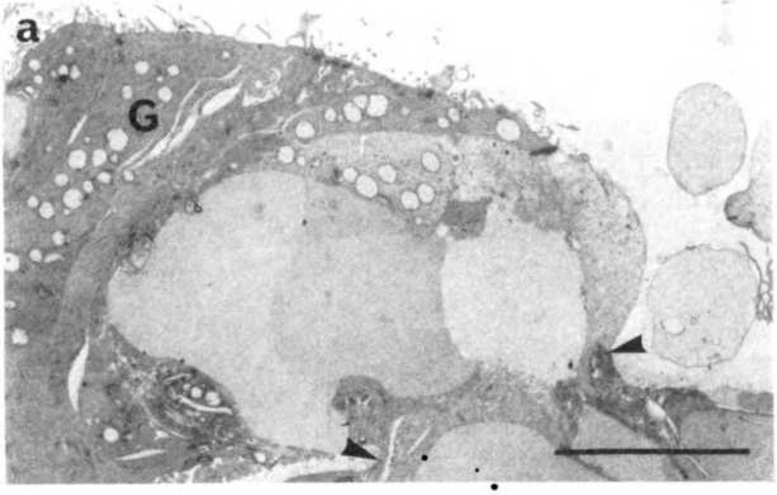

Fig. 5a *TEMs of epiretinal membranes six weeks after an injection of fibroblasts.* a: *Glial-like tissue* (G) *with surface microvilli, which had protruded through a break in the inner limiting lamina (arrowheads).* ×*2480.*

evident in the retina and epiretinal membranes up to six weeks, but by 10 weeks ^{3}H thymidine incorporation into nuclei was not common. Over the period from one to 10 weeks labelling in the majority of the cells of the epiretinal membranes was low and diffuse, but occasional cells did show high incorporation levels (Fig. 4b). The epiretinal membranes consisted mainly of glial cells, while fibroblasts and associated collagen were also noted. The glial cells were identified on the basis of their abundant cytoplasmic intermediate filaments, apical surface microvilli, and basement material (Figs. 5a, b). Adhering junctions were seen frequently joining adjacent glial cells (Fig. 5b).

RETINA

Immunohistochemical staining for actin in the retina gave a similar result to that found in the normal tissue. The inner and outer plexiform layers, the inner segments of the photoreceptor cells, and some cells in the nerve fibre layer showed a moderate positive reaction to the antiactin antibodies.

In the control retina the incorporation of ^{3}H proline was pronounced, particularly in the central retina. Uptake of label was prominent within the vasoglial connections, many cells of the inner nuclear layer and the ganglion cells (Fig. 6a). But in the experimental tissue one week after the fibroblast injection the level of proline incorporation was much lower, though some preferential incorporation was still evident. In the detached retina the label was at a very low level and was scattered diffusely throughout the various layers (Figs. 4b, 6b, c).

Three weeks after the injection of fibroblasts most

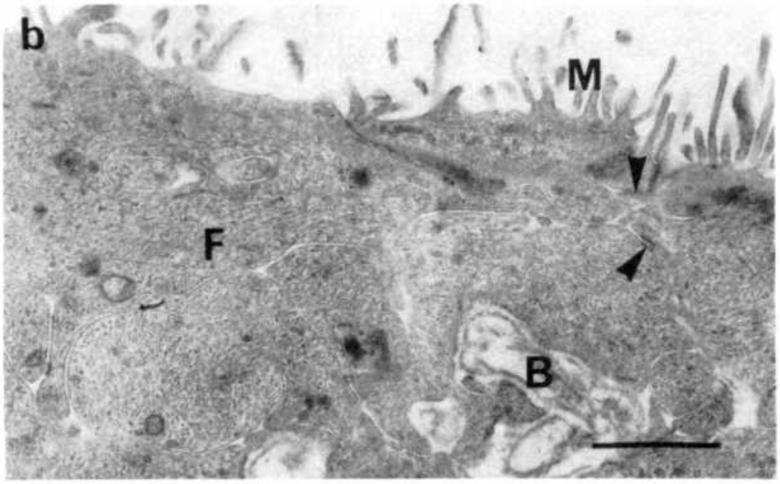

Fig. 5b *At higher power one of the cells demonstrated intermediate filaments* (F), *basement material* (B), *adhering junctions (arrowheads) as well as surface microvilli* (M). ×*16 550. Bar markers are* (a) *10* μ*m and* (b) *1* μ*m.*

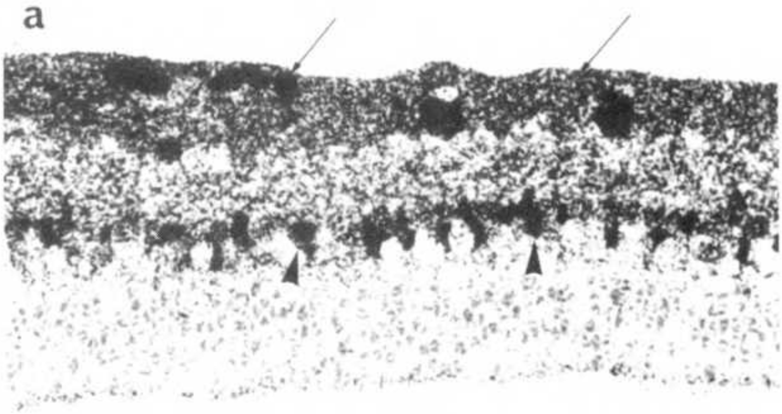

Fig. 6a *Autoradiograph of the control rabbit's retina showing the incorporation of ³H proline. Preferential uptake was visible in the inner nuclear (arrowheads), ganglion, and nerve fibre (arrows) layers.* ×355.

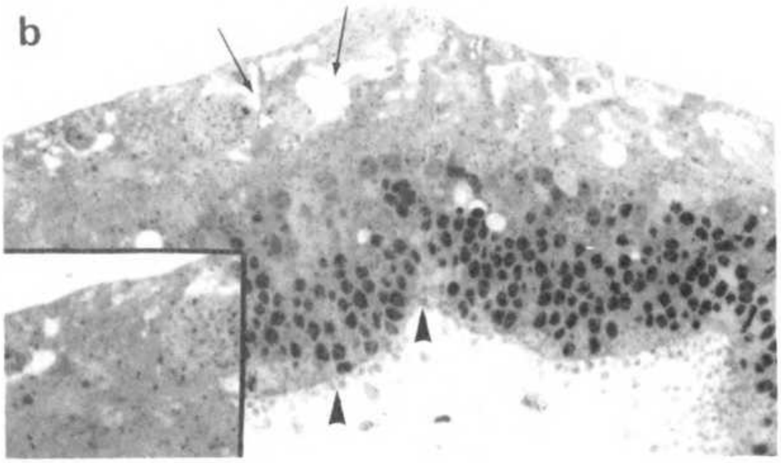

Fig. 6b *Two weeks after a fibroblast injection the outer segments could not be seen, with only remnants of the inner segments remaining (arrowheads). There were oedematous areas in the ganglion cell layer (arrows).* ×355. Insert: *High power showing evidence of proline incorporation which was of a low level.* ×515.

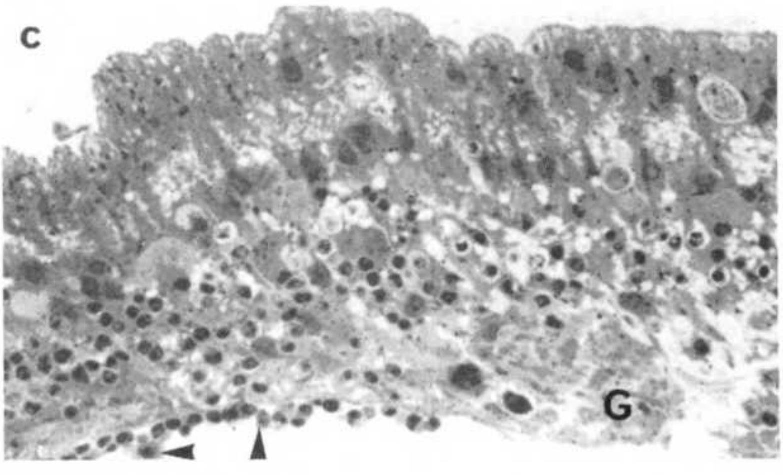

Fig. 6c *Four weeks after a fibroblast injection subretinal macrophages (the smaller migratory cells) were observed at the outer surface (arrowheads) and swelling was seen throughout the retina. Glial tissue* (G) *appeared to have proliferated on to the outer retinal surface.* ×355.

of the rabbits had a retinal detachment. By this time the most marked structural change was the gradual loss of the photoreceptor cells, which began with the loss of the outer segments and then the inner segments (Fig. 6b). A rapid decline in retinal organisation and increased oedema occurred between two and four weeks following the injection of fibroblasts (Figs. 6b, c). Oedema progressed throughout the retinal layers with the increased period of detachment.

RETINAL PIGMENT EPITHELIUM (RPE)

Following detachment of the neural retina from the pigment epithelium the RPE had lost its hexagonal arrangement (Fig. 7a) and had become rounded (Fig. 7b). The morphological alterations to the RPE increased with the duration of the retinal detachment. The apical processes had become shorter and were found on all free surfaces (Figs. 7a, b). Widening and shortening of the basal infoldings were seen, and the mitochondria were swollen (Fig. 7b). Some of the cells appeared to be more rounded or 'scalloped' than the surrounding cells. These cells gradually became detached from the monolayer (Fig. 7b). Two different sizes of migratory cells were evident in the subretinal space, and these could best be seen by SEM. The smaller cells had larger surface microvilli, which were less frequent than the small, abundant surface microvilli seen on the larger cells (Fig. 7a).

Under a detachment the 'scalloped' RPE cells and some of the larger cells in the subretinal space gave an intense positive staining reaction to prekeratin and actin (Fig. 8a). The reaction to the prekeratin antibodies was greater than that found in RPE attached to the neural retina in the normal tissue.

Both the large and small cells in the subretinal space were found to incorporate ^{3}H thymidine in their nuclei (Fig. 8b). The incorporation of ^{3}H proline in the RPE was lower than that seen in the control tissue.

SUBRETINAL MEMBRANE FORMATION

Subretinal membranes both on the exposed outer retinal surface (Fig. 8c) and on Bruch's membrane were found beneath a detached retina at various times after an injection of fibroblasts. The cells on the outer retinal surface appeared to be glia which had migrated from the retina (Fig. 8c), while the RPE cells had become elongated and several layers deep. Both the disorganised retina and the subretinal membranes showed low and diffuse levels of ^{3}H proline incorporation (Fig. 8c).

The proliferations associated with both of the retinal surfaces were found to contain rounded cells, which stained more intensely for actin than the surrounding tissue (Fig. 9a). In addition some cells within the epiretinal and subretinal membranes stained positively for prekeratin (Figs. 9b, c).

Discussion

The inflammatory response evoked in both the anterior and posterior chambers following an intravitreal injection of autologous fibroblasts has been described previously.[5,6] In the present investigation

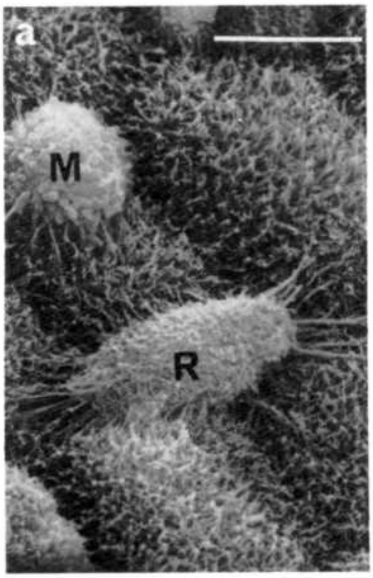

Fig. 7a *SEM of the RPE under a detached retina four weeks after a fibroblast injection. The apical surfaces of the cells had become 'scalloped'. Some of the larger cells* (R) *seemed to be detaching from the monolayer and were presumed to be RPE. Smaller migratory cells* (M) *with large microvilli were also seen.* ×*1855.*

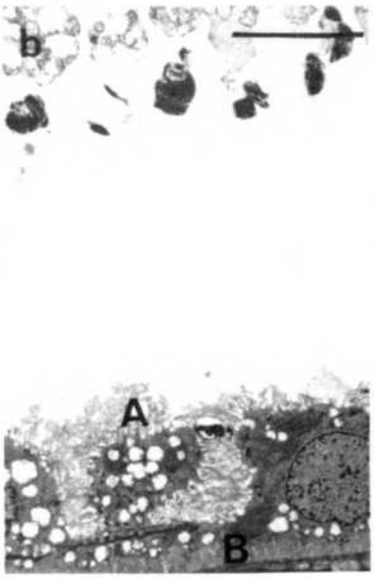

Fig. 7b *TEM of a scalloped RPE layer beneath a detached retina six weeks after an injection of fibroblasts. The cells had abundant and disorganised apical processes* (A), *while the basal portion* (B) *had widened and shortened infoldings.* ×*1630. Bar markers are* (a) *10 µm and* (b) *10 µm.*

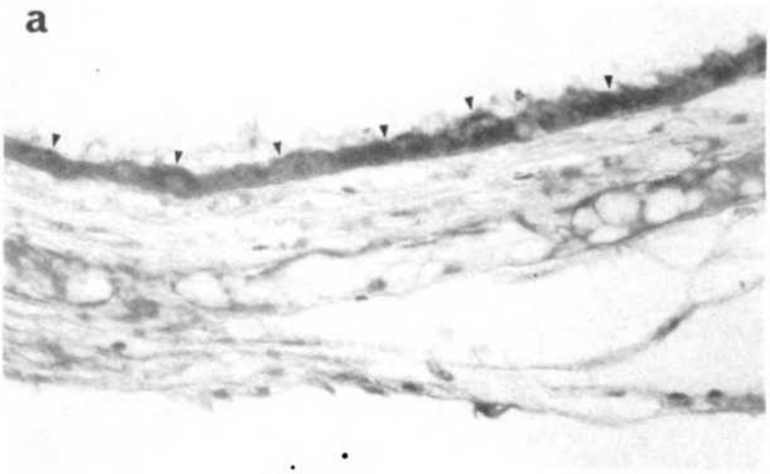

Fig. 8a *The RPE (arrowheads) under a detached retina stained positively for prekeratin when stained by an indirect immunoperoxidase technique. ×355.*

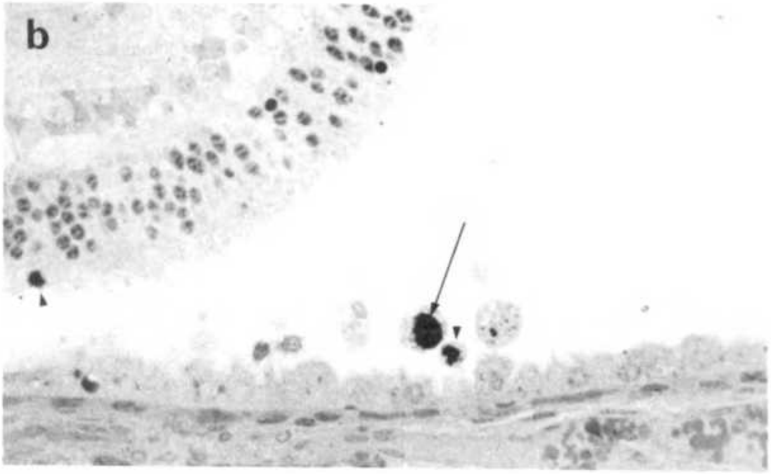

Fig. 8b *Autoradiograph of ^3H thymidine within the nuclei of both the large (arrow) and small (arrowheads) subretinal, migratory cells. ×395.*

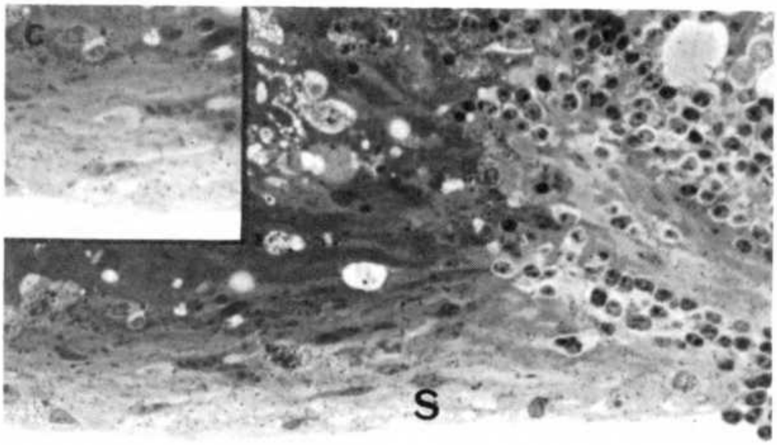

Fig. 8c *Autoradiograph showing a diffuse pattern and low level of ^3H proline incorporation within a subretinal membrane* (S), *four weeks after a fibroblast injection. ×475.* Insert: *High power showing silver grains of proline incorporation. ×595.*

the inflammatory cell infiltrate was found to gain entry into the vitreous via the pars plana and the vascular complex associated with the optic nerve head. Inflammatory cells were found also within the choroid and beneath the detached retina.

The formation of new vessels within the vitreal proliferations[5] and in the optic disc region[10,11] was most likely to have been promoted by the release of 'angiogenic' or 'vasoproliferative' factors arising from retinal ischaemia,[14-16] though other factors may have been involved.

The structural changes within the vessels and the perivascular cells were characteristic effects of ischaemia.[17] The accumulation of basement material around the vessels implied endothelial cell degeneration and regeneration with secondary pericyte degeneration.[18,19] The low levels of ^{3}H proline incorporation in perivascular cells is difficult to interpret. These were not 'pulse chase' experiments, so that we do not know whether the low levels represented a rapid turnover of radiolabelled proline or a poor uptake. However, there is undoubtedly a change in metabolic activity in comparison with the perivascular cells in the control tissue.

The development of both epiretinal and subretinal membranes was observed after an intravitreal injection of fibroblasts; these proliferations were associated with a tractional retinal detachment. Fibroblast-like cells, glial-like cells, epithelium-like cells, and collagen were identified within the epiretinal membranes. Indeed low levels of ^{3}H proline were seen within all the cell types associated with the epiretinal membranes. However, the level of incorporation was low, though new collagen was seen in many of the epiretinal membranes examined. This unexpected result could be explained by the time of proline administration being too late, that is, beyond the time when collagen precursors were being synthesised.

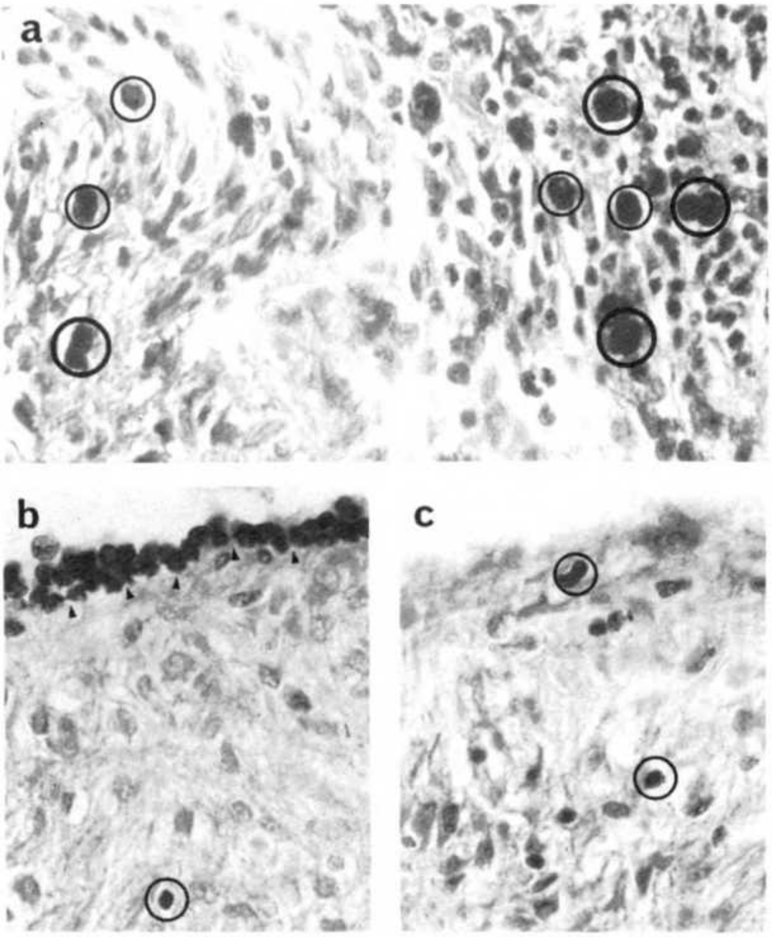

Fig. 9 a: *Some large migratory cells (circled) within an epiretinal membrane were found to stain strongly for actin (counterstained with haematoxylin).* ×*510.* b and c: *Some of the migratory cells (circled or arrowheads) within epiretinal membranes were found to stain positively for prekeratin (no counterstain). Immunohistochemical staining by the peroxidase-antiperoxidase technique.* ×*510.*

The glial cells which had migrated on to the retinal surfaces had abundant cytoplasmic filaments similar to fibrous astrocytes, but the cells tended to be plate-like or spindle-shaped. Green[20] described glial cell proliferation as a 'reparative and degenerative process' In the present study glial cells were seen on the exposed outer retinal surface. It seemed likely that Müller cells formed these subretinal proliferations, as they were plate-like cells similar to those described by Burke and Foster when cells from the retina were grown in culture.[21] The migration of accessory glia through the retina to the subretinal space seemed an unlikely event.

The protrusion of retinal cells on the inner retinal surface has also been suggested to be a reparative response to breaks in the ILL, caused by substances 'foreign' to the vitreous.[22] Grierson and Forrester[3] proposed that the release of lytic enzymes, from intravitreally injected fibroblasts which had died, caused the rupture of the vitreous face, resulting in posterior vitreous detachment, thus ensuring the availability of the retinal surface as a scaffold for cell migration and proliferation. Nevertheless we found that, although the injection of fibroblasts caused posterior detachment and liquefaction of the vitreal gel, damage to the ILL on the vitreal surface was not seen. In contrast the bulges seen on the retinal surface appeared to originate from beneath the ILL, which indicated that the retinal cells were pushing their way through. Eventually cells were observed to come through the subsequent deficits in the ILL and then were able to migrate and proliferate on the inner retinal surface to form epiretinal membranes. When the retinal cells initially began to protrude through the ILL, they had many cytoplasmic processes and intermediate filaments and hence were similar to fibrous astrocytes. As the membranes developed, the glial cells had become plate-like or spindle-shaped but still retained a cytoplasmic content analogous to fibrous astrocytes, that is, abundant cytoplasmic filaments with few organelles.[23 24] Once the epiretinal and subretinal membranes had developed, the retinal glia within these proliferations had altered in shape from astrocytic to plate-like or spindle-shaped cells. A similar change in shape was shown by Duffy *et al.*[25] to occur in tissue cultured astrocytoma cells. Hence the movement of the glial cells from the neural layers of the retina may have caused their structural alteration.

Unfortunately, morphology alone was not sufficient to reveal the definitive type of glial cell within the membranes. Even though it is difficult to imagine how Müller cells can migrate out of the retina, we consider that this study has provided further evidence to indicate that such is the case in the epiretinal membranes found in the peripheral retina. Firstly, the protrusions on the inner retinal surface which were seen in the initial stages of epiretinal membrane formation were far too numerous for them to be astrocytic glia. Indeed it was shown previously that only the medullary ray areas of the rabbit retina contained astroglia, whereas Muller cells were identified throughout the retina.[26] Secondly, the majority of ^{3}H thymidine incorporation within the retina was located in the inner nuclear layer, implying DNA synthesis within the Müller cell nuclei which are situated there. On the other hand the possibility of astrocytic glia being involved in epiretinal membranes in the medullary ray areas could not be dismissed.

Sternberg and Machemer[27] suggested that human subretinal membranes were composed mainly of pigment epithelial cells, whereas glial cells were prominent in subretinal membranes produced in experimental animals models. In the present study glial cells were identified histologically within the subretinal membranes which developed after an intravitreal injection of autologous fibroblasts. In addition the membranes were shown definitively to contain cells which stained for the presence of prekeratin. Runnger-Brändle and Gabbiani[28] described prekeratin as a cytoskeletal protein found in cells of an epithelial origin, and thus the positively stained cells were identified as epithelial cells.

Both the incorporation of ^{3}H thymidine and the observation of cells detaching from the RPE monolayer gave further evidence of the involvement of the RPE cells in the subretinal proliferation.

Many non-muscle cell types have been shown to contain actin, and its presence has been linked with such roles as cell division and locomotion.[29] In the retina of the experimental tissue some staining for actin was seen, but the most intense reactions were seen in the free and migratory subretinal cells and some cells within the epiretinal and subretinal proliferation. The cells within the proliferative tissues which stained more intensely for actin than the surrounding elongated glial cells resembled the migratory cells seen in the subretinal space.

The source of the migratory cells could not be identified with certainty from the histological observations, that is, whether the cells were macrophages from the choroid or detached RPE cells. Previous experimental models have described histologically the presence of pigment epithelial cells, fibroblast-like cells with additional epithelial characteristics, and pigment epithelial macrophages within intraocular proliferations associated with a rhegmatogenous retinal detachment.[30] The process by which a 'normal' retinal pigment epithelial cell alters to become a fibroblast or macrophage-like cell has been described as 'metaplasia' or 'transformation' by others.[31–33] On the other hand cells of haematogenous origin have been seen to migrate from the choroid to the vitreous following injury to the vitreous[34] and retina.[35] However, we have shown immunohistochemically the presence of large, rounded cells which stained positively for the presence of prekeratin and therefore were identified as epithelial cells. Hence a proportion of the rounded migratory cells within the retinal proliferations was apparently of an epithelial origin. Therefore some of the largest migratory cells, which have been seen in the past within the retina,[34–36] and within periretinal proliferations in the present study, were identified by immunohistochemistry as cells of an epithelial origin. However, other cells both within the retinal proliferation and the subretinal space were identified as 'true' macrophages (of reticuloendothelial origin) on the basis of their smaller size and their surface microvilli, which differed from those of the RPE. A proportion of both the larger rounded RPE cells and the inflammatory cells stained for actin and incorporated ^{3}H thymidine. The detached retinae which occurred in all the rabbits' eyes following an intravitreal injection of fibroblasts showed pathological changes associated with ischaemia which were similar to those described by Johnson[17] and Johnson and Foulds.[17]

The overall deterioration of the detached retina was mirrored by the very low and diffuse levels of ^{3}H proline incorporation which were seen in comparison with the normal tissue. Depression of proline incorporation within the Muller cells is consistent with their loss of function during prolonged periods of retinal detachment. The results compared favourably with those of Machemer and Buettner[38] when the differences in technique, dosage, and isotope are taken into account.

The morphological changes seen within the RPE following retinal detachment induced by the injection of fibroblasts were similar to the changes found after high pressure induced ischaemia[17] and experimental retinal detachment[38] in the rabbit The nuclear incorporation of ^{3}H thymidine within the attached and detached RPE cells provided evidence of DNA synthesis DNA synthesis has also been demonstrated in the RPE of the owl monkey[30] and cat[39] following retinal detachment. Anderson *et al.*[39] believed that the loss of metabolic exchange between the separated neural retina and RPE brought about the 'dedifferentiation' and proliferation of the RPE cells.

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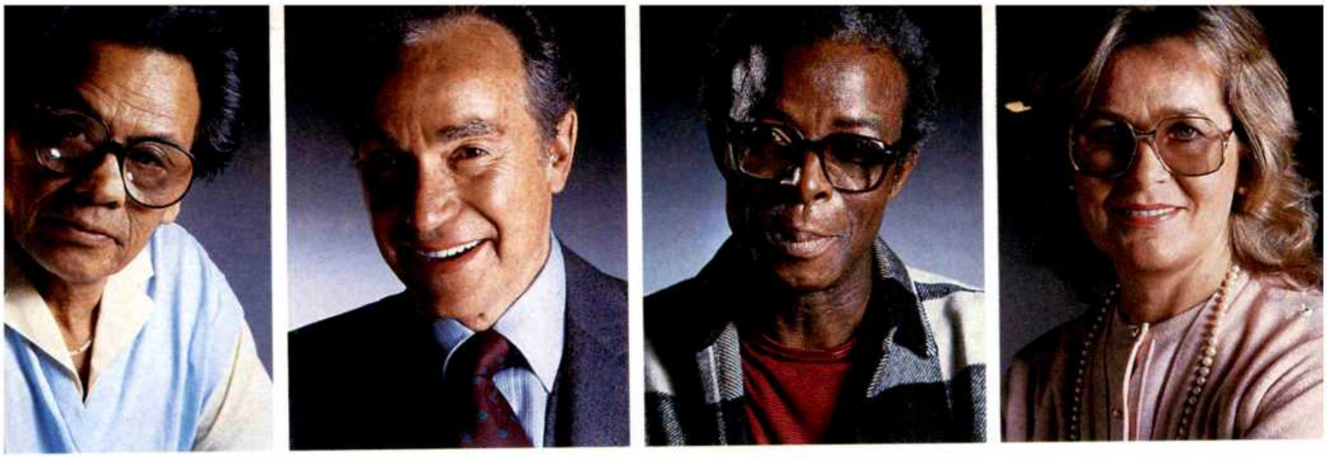

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Perforating eye injuries caused by darts

M D COLE AND D SMERDON

From the Birmingham and Midland Eye Hospital

SUMMARY We have reviewed 19 patients with dart-induced perforating eye injuries. Fourteen of the injuries were in childhood. A poor visual outcome was common, not only from the injury directly but also from irreversible amblyopia or endophthalmitis. Preventive measures are considered.

Darts are responsible for the largest single group of childhood perforating eye injuries.[1] To find ways in which this type of injury can be prevented, we have analysed a group of patients who have sustained dart-induced perforating eye injuries. Our aims were to determine the incidence, mode, and type of injury and the eventual visual outcome.

Materials and methods

Theatre registers from the Birmingham and Midland Eye Hospital were used to identify all cases of perforating eye injuries between 1 September 1977 and 30 June 1985. The corresponding medical records were examined.

All patients with dart injury were recalled for examination so that the histories could be verified, and the final visual outcome determined. This gave a minimum of 12 months' follow-up for the 15 who attended.

The following details were recorded: Age and sex, place injury occurred, time taken to reach the casualty department, mode of injury, part of dart involved, pattern of injury, and outcome.

Results

The records of 436 patients were reviewed. They represented a 97% retrieval. Of these patients 375 patients sustained perforating eye injuries, 19 of which were caused by darts (5%). Of these, 15 attended for reappraisal (80%).

The results are summarised in Tables 1 and 2 and analysed below.

There were 78 (20·8%) childhood injuries (defined as those injuries occurring under the age of 14 years), 14 of which (18%) were caused by darts.

The male to female ratio for dart injuries was 2·8:1 (14:5).

Of the 19 injuries, 18 occurred in the patient's or a friend's home. One injury occurred in a boys' club.

We looked specifically at the delay between injury and hospital attendance and found that five patients took longer than 12 hours to attend. All of these

Table 1 *Case history*

Patient no	*Age*	*Sex*	*Eye*	*Dart end*	*Cause*	*Delay**
1	7	M	R	Point	Playing	—
2	3	M	R	Point	Playing	?
3	4	M	R	Stem	Pull out	—
4	4	F	R	Point	Throw	48 h
5	15	M	R	Flight	Pull out	18 h
6	4	F	R	Point	Threw	?
7	17	M	R	Point	Threw	—
8	10	M	L	?	Pull out	?
9	3	F	R	Point	Threw	—
10	7	M	L	Point	Threw	12 h
11	18	F	R	Point	Pull out	12 h
12	6	M	L	Point	Playing	?
13	9	M	R	Flight	Aiming	?
14	24	M	R	Flight	Pull out	24 h
15	11	M	R	Flight	Pull out	—
16	10	M	R	?	Rebound	16 h
17	2	M	L	Flight	Pull out	?
18	3	F	L	?	Play	—
19	12	M	R	Flight	Pull out	—

*Delay quoted if ≥12 hr

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Table 2 *Injury and outcome*

Patient no	*Follow-up, yr*	*Lid injury*	*Wound site*	*Complications*	*VA*
1	0 33	Upper	Sclera	Chorioretinal scar	6/12
2	0 66	Nil	Limbus	?	?
3	8	Nil	Cornea	Esotropia/amblyopia	HM
4	8	Nil	Limbus	Chorioretinal scar	6/6
5	7	Nil	Cornea	—	6/6
6	7	Nil	Cornea	Esotropia/amblyopia	CF
7	7	Upper	Sclera	—	6/6
8	1·33	Nil	Cornea	—	6/5
9	7	Nil	Cornea	Amblyopia	HM
10	7	Upper	Cornea	Esotropia/phthisis	NPL
11	6	Nil	Cornea	—	6/6
12	0 06	Upper	Cornea	—	6/6
13	5	Nil	Cornea	—	6/5
14	4	Nil	Cornea	—	6/5
15	4	Nil	Limbus	—	6/5
16	3	Nil	Cornea	Esotropia	6/18
17	3	Nil	Cornea	Amblyopia	6/60
18	2	Nil	Cornea	Exotropia/ambolyopia	6/9
19	1 5	Nil	Cornea	Vitrectomy/macular scar	6/36

HM=hand movements NPL=no perception of light

Table 3 *Results of lensectomy*

Patient no	*End*	*Age (yr)*	*Procedure*	*CL*	*Amblyopia*	*VA*
3	Flight	3	Secondary + AV	CL(Ab)	Amb	HM
6	Point	4	Secondary + AV	CL(Ab)	Amb	CF
9	Point	3	Secondary + PK	—	Amb	HM
10	Point	7	Secondary + AV	—		NPL
11	Point	24	Primary + AV	CL(Ab)		6/6
16	?	10	Primary + AV	CL		6/18
17	Flight	2	Primary	CL	Amb	6/60
18	?	3	Secondary	IOL	Amb	6/9
19	Flight	12	Primary + AV	CL		6/36

AV=anterior vitrectomy CL=contact lens Ab=abandoned HM=hand movements CF=counting fingers NPL=no perception of light

patients felt that at the time the injury was not serious and attended only because of symptoms of blurred vision, watering, and pain in the eye.

There were eight self-inflicted injuries, seven of which occurred while pulling the dart out of the target (five dart boards, one calendar, and one toy elephant). This was caused by either pulling the flight end into the eye or by dropping the dart. One injury was caused by drawing the flight end of the dart into the eye while taking aim.

The dart was thrown by a friend or sibling in seven cases. One injury resulted from the dart rebounding off the board, and the remaining four resulted in an uncertain manner from childhood play.

There were nine injuries which resulted by the pointed end entering the eye and seven by the flight end (one with the flights removed). The remaining three patients did not know which end was responsible.

There were four whose injury was caused by the point penetrating the upper lid (two scleral and two corneal perforations).

The injuries were divided into 17 small (4 mm or less) and 2 large (>4 mm) injuries. All these injuries were linear. There was no specific pattern to the wounds, except that flight-end injuries tended to have larger surface and smaller endothelial wounds. The perforations were mainly corneal (14), but three were limbal and two were scleral.

Significant lens injury was found in nine patients and insignificant injury in two (localised anterior subcapsular lens opacity, which did not progress or affect acuity). Of those with significant lens injury four had a primary and five had a secondary lens extraction, with six requiring an anterior vitrectomy.

Aphakic correction was by contact lens in six patients (three later abandoned them), and one 3-year-old child was corrected with an intraocular lens inserted after secondary lensectomy. No correction was given to two patients, one awaiting penetrating keratoplasty and one who developed endophthalmitis with phthisis bulbi (Table 3). Lens damage was caused as often by the flight end as the pointed end of the dart.

We looked specifically at strabismus, amblyopia, and eventual visual acuity. A secondary horizontal squint was found in five patients (four convergent, one divergent). Amblyopia developed in five patients aged under 5 years after lens extraction which required occlusion therapy. Of these patients four had contact lens correction, but all resulted in a poor visual outcome (<6/36). An intraocular lens was used for a 3-year-old which gave a visual outcome of 6/9. There were peripheral chorioretinal scars in three patients. These did not cause secondary retinal problems and included both cases with scleral wounds.

Postoperative endophthalmitis ensued in two patients (10·5%). One eye became blind and phthisical and the other survived after vitrectomy, achieving a visual acuity of 6/36. We were unable to establish whether the macular scar found subsequently was due to the original injury.

Table 4 *Visual outcome*

Visual acuity	*No of patients*
6/5–6/6	8
6/9–6/12	1 (Amblyopic)
6/18–6/24	1 (?)
6/36–6/60	2 (1 Macular scar, 1 amblyopic)
<6/60–PL	3 (All amblyopic, one graft failure also)
NPL	1 (Phthisis from endophthalmitis)

The eventual visual acuity of 16 patients with a follow-up of greater than 12 months was assessed (Table 4). A final acuity of 6/6 or better was seen in eight patients. One had no perception of light and seven had acuities between these extremes; five had amblyopia, one had a macular scar, and in one the reason for a poor acuity was not explained satisfactorily.

Discussion

Various authors[3-5] have included darts as a cause of perforating eye injury in children. Roper-Hall[6] stressed that toys had proved to be unexpectedly dangerous, and we agree with this. Children are notorious for the wide variety of objects which they manage to stick in their eyes,[1] and it is difficult to pinpoint ways in which these injuries can be prevented. It is only the latest series of perforating eye injuries by Cole *et al.*[1] that emphasises that darts are the commonest cause in children, as the present study confirms.

The perforations are usually small and the patient may not appreciate how serious the injury is, especially if the pointed end of the dart went through the eyelid. This may lead to delay in attending the casualty department, which contributes to the risk of endophthalmitis.

Amblyopia is a prominent factor in poor visual outcome. In this study 10 patients were aged under 8 and thus prone to developing amblyopia. All those under 8 who required lens surgery (excluding the patient who became blind from endophthalmitis) became amblyopic. This was reversed in only one patient, whose aphakia was corrected with an intraocular lens. Treatment was particularly unsatisfactory in one child who had both failed penetrating keratoplasty and failed trabeculectomy. Eagling[7] also found that the perforating eye injuries in this age group requiring lens surgery usually suffered from irreversible amblyopia, even with immediate lens surgery (with or without an intraocular lens), as it is difficult to achieve clear media within two months of the injury.

Darts are capable of causing an injury with either end. Even with the flights removed the shaft can still cause injury. It is not generally appreciated how dangerous darts can be. This was shown by the two 17-year-old friends who threw darts directly at each other for fun (patient no. 7). However, the problem must be considered in perspective. Some five million people play darts regularly (Lowy SR, personal communication, 1986), and the game when played properly is very safe. All but one of the injuries occurred in the home, and 14 out of 19 were childhood injuries.

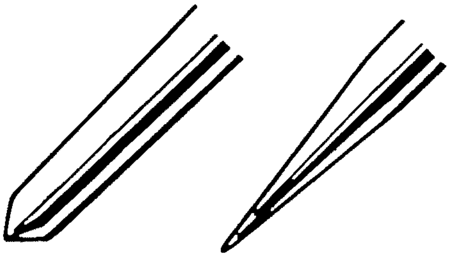

Fig 1 *Dart ends illustrating the safer point.*

Preventive measures can help to reduce the incidence of injuries The most recent example of this is the influence of seat belt legislation on perforating eye injuries.[8]

We consider that all adults, and especially parents, should be encouraged to consider darts an adult game. A major manufacturer of darts print in their catalogue to retailers (Lowy SR, personal communication, 1986). 'To our customers. Warning. Darts is an adult sport It is dangerous for children to play without supervision. We recommend that a dealer should exercise discretion where any sale might result in children playing without adult supervision.' On every set of darts that they sell they print in six languages—English, French, German, Spanish, Arabic, and Japanese—the following: 'Darts is an adult sport. It is dangerous for children to play without supervision.'

Certain dart manufacturers design their dart points in such a way that they will penetrate the dartboard without difficulty but are much less likely to pierce the skin than a conventionally designed point (Fig. 1). This may influence the likelihood of perforation of the globe. In view of the rather surprising number of injuries caused by the flight end, it may be possible to design safer darts. Dart flights need to be fairly stiff to maintain a consistent trajectory, but they do not need to be sharp or pointed.

The British Standards Institution has published several standards that deal with the safety of toys (Hall AJ, personal communication, 1986). The following paragraph (3.2.2.10.3) applies to darts for children: 'The points of darts for children shall not be made of metal; points fitted with magnetic discs are permitted.'

We consider that this clause should include guidelines for the production of flights. As the British Standard is being revised, this survey has been submitted to the committee responsible for consideration.

The consumer unit of the Department of Trade and Industry has also studied the results of our survey

(Loughlin TRJ, personal communication, 1986) and forwarded a copy to the British Sports and Allied Industries Federation, who represent dart manufacturers. The consumer unit has recommended that 'the packaging of adult darts should contain a warning against allowing children under 14 years to use them unsupervised.' They have also suggested that dart manufacturers 'should consider carefully the design of flights so that they avoid sharp tails and sharp points at the rear of the dart.'

CONCLUSION

Adult-type darts must not be considered as toys, and the unsupervised use of darts by children must be discouraged. Manufacturers must be encouraged to consider ocular safety when designing their darts.

We thank the consultants in the Birmingham and Midland Eye Hospital for permission to report their cases; and Miss E M Eagling and MRS J E Cole for their kind help and advice in the preparation of this paper

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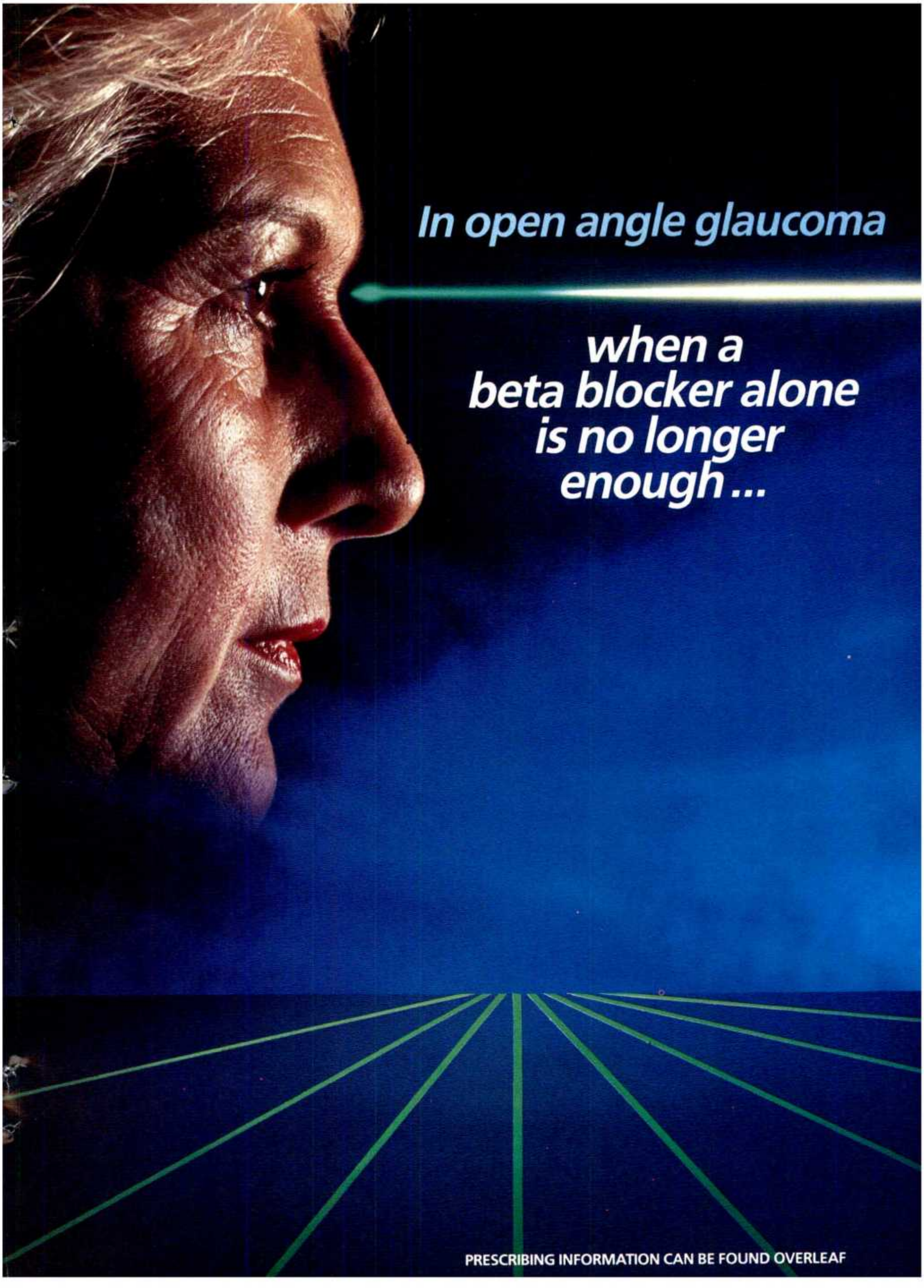
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The one-and-a-half syndrome. Clinical correlation with a pontine lesion demonstrated by nuclear magnetic resonance imaging in a case of multiple sclerosis

C N MARTYN AND D KEAN

From the University Departments of Medicine and Radiology, Royal Infirmary, Edinburgh

SUMMARY Nuclear magnetic resonance (NMR) imaging has been used to visualise a localised area of demyelination in the dorsal pons of a patient who presented with an unusual disorder of eye movements, namely, the one-and-a-half syndrome. Judged clinically the patient made a nearly complete recovery, but little change was apparent in the NMR image six months later.

The unusual and remarkable disorder of eye movement consisting of a lateral gaze palsy in one direction and an internuclear ophthalmoplegia in the other was probably first described by Freeman *et al.*[1] and later dubbed the one-and-a-half syndrome by Fisher.[2] In the fully developed syndrome one eye is in the midline and completely fails to move horizontally while the other can only abduct. Fisher attributed the syndrome to a single unilateral lesion affecting the centre for conjugate lateral gaze in the paramedian pontine reticular formation and the adjacent ipsilateral medial longitudinal bundle. This anatomical localisation has been confirmed at necropsy in several cases. Recorded causes of the syndrome include tumour, trauma, infarction, haemorrhage, and demyelination.[3,4] We report a further case, occurring in a patient with multiple sclerosis, in which the lesion was successfully visualised during life by magnetic resonance imaging.

Case report

A 30-year-old woman presented with a two-week history of diplopia, unsteadiness of gait, and altered taste sensation. She had noticed, too, that her face had become asymmetrical. Examination revealed a complete horizontal gaze palsy to the left for voluntary and tracking eye movements and also for reflex eye movements in response to head turning. A contralateral internuclear ophthalmoplegia was present: the left eye failed to adduct past the midline, and horizontal jerking nystagmus was apparent in the abducting right eye. Up-gaze was incomplete with gaze-evoked upbeat nystagmus, and convergence was impaired. Figs. 1–3 illustrate the horizontal gaze palsies. There was an incomplete left-sided facial palsy of lower motor neurone type, and taste sensation was lost on the left side of the tongue. Abdominal reflexes were absent, and both plantar responses were equivocally extensor.

Eight years earlier she had been investigated extensively but inconclusively for an episode of bilateral foot drop associated with paraesthesiae

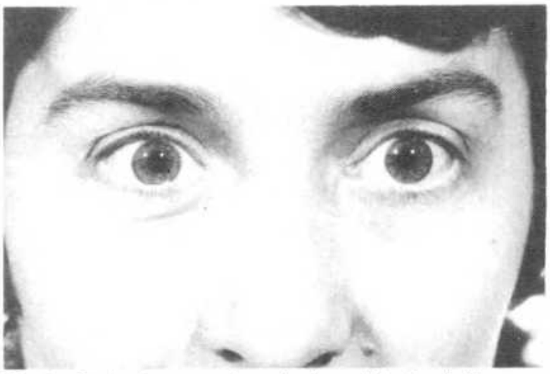

Fig. 1 *Patient is attempting to look straight ahead. No abnormality of conjugate gaze is apparent.*

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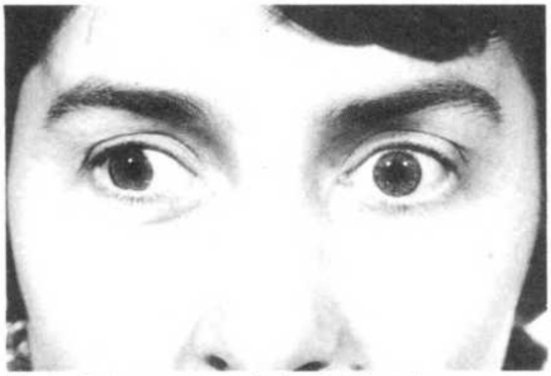

Fig. 2 *Patient attempts to look right. The right eye abducts, but the left remains fixed at the midline.*

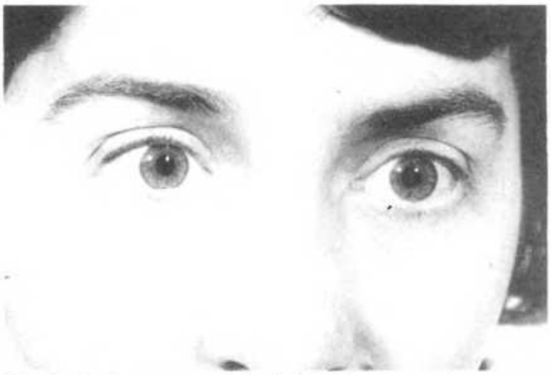

Fig. 3 *Patient attempts to look left. There is no movement of either eye.*

affecting both lower limbs. Myelography had been normal and no abnormalities in the cerebrospinal fluid (CSF) had been detected. She had recovered fully within three months. Four years later she had experienced paraesthesiae and weakness affecting the whole of her left arm in association with difficulty in manipulating small objects with her left hand. No investigations had been undertaken, but she again made a full recovery within a few months. While this report was being prepared she sustained a typical attack of left-sided retrobulbar neuritis.

Investigations during her most recent illness were as follows: erythrocyte sedimentation rate 11 mm/h, antinuclear factor test negative, DNA binding <5 units/ml (normal less than 25 units/ml), Mantoux test positive at 1:1000, VDRL and TPHA tests for syphilis negative on both blood and CSF, serum B_{12} and folate normal. CSF protein was 282 mg/l and oligoclonal bands were not detected. The CSF cell count was $1/\text{mm}^3$. The CT brain scan was normal, and there were no abnormalities on chest *x*-ray. Visually evoked responses to a reversing checker board stimulus demonstrated a delay of the P100 wave in the right eye of 18 ms relative to the left.

Nuclear magnetic resonance imaging was performed on a low field (0·08T) resistive MR system[5,6] with a TR (repetition rate) of 1 second and a TI (time from inversion) of 200 ms. Lesions such as those found in demyelinating conditions produce an elevation in magnetic relaxation times and were clearly shown by NMR.[5] Figs. 4 and 5 are T_1 weighted images which show a left-sided abnormality in the lower

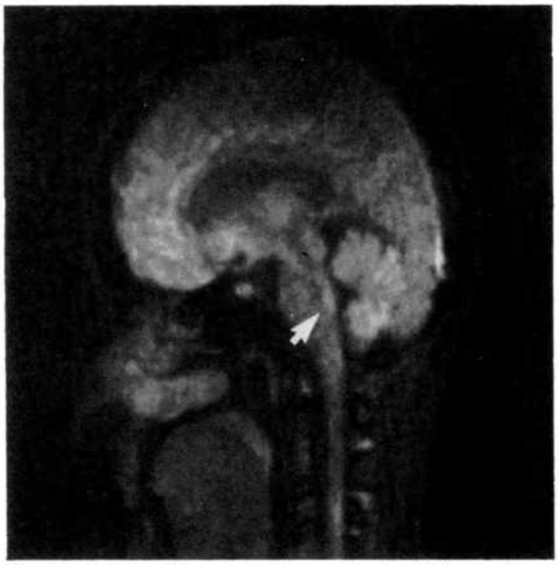

Fig. 4 *A sagittal T_1 weighted image showing high signal from the area of pontine demyelination.*

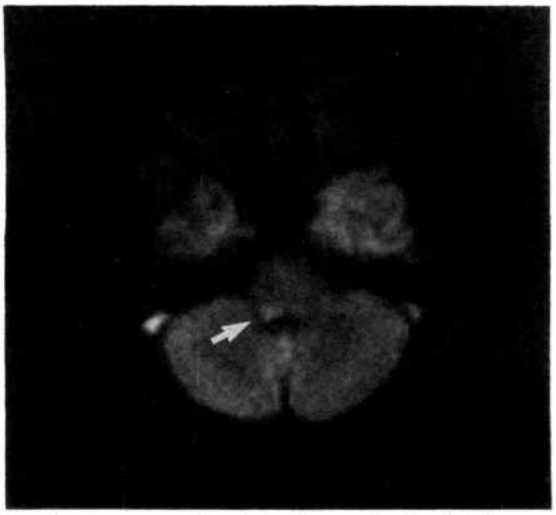

Fig. 5 *A transverse T_1 weighted image showing that the lesion is confined to the left side of the dorsal pons.*

pontine tegmentum. This area of prolonged T_1 is typical of an area of demyelination.

The patient was treated with dexamethasone 8 mg/day for five days. Her facial palsy, loss of taste, and internuclear ophthalmoplegia recovered gradually over the next month. After six months her only remaining abnormality was vertical nystagmus on upgaze. She was re-examined by NMR, which, despite the clinical improvement, showed little change.

Discussion

This woman has sustained four episodes of neurological disturbance in the past nine years, recovering completely or nearly completely from each. There has never been any clinical or laboratory evidence of an arteritic condition or of sarcoidosis. Although there are no typical abnormalities in the CSF, the diagnosis is almost certainly multiple sclerosis.

The one-and-a-half syndrome is thought to be caused by a lesion in the lower pontine tegmentum affecting the sixth nerve nucleus and the lateral gaze centre in the adjacent paramedian reticular formation as well as the ipsilateral median longitudinal fasciculus. In this case the facial weakness and disturbance of taste indicate that the seventh nerve nucleus and the rostral part of the nucleus of the tractus solitarius, or alternatively the infranuclear fibres of the facial nerve and nervus intermedius as they pass through the pons, were also affected. A small lesion affecting exactly this area is clearly demonstrated by nuclear magnetic resonance imaging. This case shows the value of magnetic resonance imaging techniques in the investigation of brain stem lesions. Not only has it been possible to localise the lesion producing this unusual combination of disorders of eye movements within the pons but information about the pathology of the lesion has been provided. NMR allowed a definite diagnosis to be reached during the acute phase of the illness without recourse to invasive investigations.

We are grateful to Dr M A Smith, Miss R A B Douglas, and Mrs A Blanc, of the NMR Imaging Unit, Royal Infirmary, Edinburgh, for their help with this case.

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Single-dose cefotaxime intramuscularly cures gonococcal ophthalmia neonatorum

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SUMMARY Nine neonates with culture proved gonococcal ophthalmia neonatorum were treated with a single intramuscular injection of 100 mg/kg of cefotaxime without topical antibiotic therapy. Five of the nine strains were penicillinase-producing *Neisseria gonorrhoeae*. All nine cases were clinically and microbiologically cured, and no side effects were observed.

Gonococcal ophthalmia neonatorum ceased to be a public health problem once silver nitrate ocular prophylaxis was systematically introduced early this century. In industrialised countries the condition lost its blinding character in the 1940s when penicillin became generally available.

With the emergence and spread of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) strains since 1976[1] other antibiotics such as the third generation cephalosporins and kanamycin were introduced for the treatment of these infections.[2-5] The prevalence of PPNG strains remains low in industrialised countries, but in the developing world, in particular in South-east Asia and Africa, they account for up to 20 to 80% of circulating gonococcal strains.[6] Hence gonococcal ophthalmia neonatorum may again become a blinding disease in these parts of the world unless effective and simple treatment schedules are available.

This study reports the results of treating gonococcal ophthalmia neonatorum with a single dose of cefotaxime 100 mg/kg intramuscularly.

Material and methods

Cases of gonococcal ophthalmia neonatorum seen at the paediatric outpatient department of Kigali Hospital, Rwanda, Central Africa, during the year 1985 are included in this study.

In neonates with purulent conjunctivitis a presumptive clinical diagnosis was confirmed by Gram stain and culture for *N. gonorrhoeae* on modified Thayer-Martin medium. All nine cases included had a positive culture, and all strains were tested for β-lactamase production by the chromogenic cephalosporin test. Three cases were referred from peripheral health units and had received antibiotic therapy.

The patients were treated with a single intramuscular injection of cefotaxime 100 mg/kg, without topical antibiotics. Mothers received a single dose of spectinomycin 2 g intramuscularly as epidemiological treatment.

The infants were examined by an ophthalmologist (KP) before and after treatment to monitor eventual corneal complications. A follow-up examination was planned for 3 and 7 days after the day of treatment, and conjunctival swabs were taken for control cultures.

Results

Characteristics of the nine patients and results of antimicrobial therapy are summarised in Table 1. Their ages ranged from 2 to 36 days with a median age of 9 days. Four infants were male and five female. All the patients presented with a purulent ocular discharge, which was bilateral in seven of the nine. One presented with gonococcal ophthalmia neonatorum and a purulent otitis media; cefotaxime treatment was continued for five days in this case.

Five out of the nine isolates proved to be PPNG strains. All nine patients were clinically cured without any residual eye damage. Moreover, all follow-up cultures were negative for *N. gonorrhoeae*.

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Table 1 *Gonococcal ophthalmia neonatorum treated with cefotaxime 100 mg/kg single dose intramuscularly: characteristics of patients and treatment results*

Case	*Age (days)*	*Sex*	*Weight (kg)*	*Clinical features*	*Previous therapy*	*β-lactamase*	*Follow-up*	
							Clinical	*Culture*
1	13	F	3·4	Bilat	—	−	Cured (day 3)	Neg (day 3)
2	13	F	2·3	Bilat.	Penicillin IM for 6 days	+	Cured (day 2 and 7)	Neg (day 7)
3	2	F	1·6	Bilat	—	+	Cured (day 2, 5 and 7)	Neg. (day 2 and 7)
4	7	M	2·0	Bilat *	Penicillin IM for 4 days + chloromycetin eye ointment	+	Cured (day 4 and 6)	Neg (day 6)
5	8	F	3·3	Unilat	—	+	Cured (day 4, 7, and 11)	Neg (day 4 and 7)
6	17	M	2·8	Bilat	Tetracycline eye ointment	−	Cured (day 3)	Neg (day 3)
7	36	M	3·4	Bilat	—	−	Cured (day 4)	Neg. (day 4)
8	9	M	2·9	Bilat	—	+	Cured (day 3 and 8)	Neg (day 8)
9	11	F	3·15	Unilat	—	−	Cured (day 5)	Not done

*Plus right purulent otitis media (culture negative on day 0), received cefotaxime 100 mg/kg/day intramuscularly in two doses for five days.

Discussion

These data show that cefotaxime in a single intramuscular injection of 100 mg/kg without topical antibiotic therapy effectively cures gonococcal ophthalmia neonatorum due to PPNG and non-PPNG strains.

It has been demonstrated that gonococcal ophthalmia neonatorum should be treated by systemic antibiotics either alone or in combination with local treatment, but not by local therapy alone.[7] Until recently penicillin was the treatment of choice worldwide, and a schedule of aqueous benzylpenicillin, 50 000 units/kg/day given intravenously in two doses for seven days with admission of the neonate to hospital was recommended.[8]

Following the emergence of PPNG strains cases of gonococcal ophthalmia neonatorum due to these strains have been reported. So long as the prevalence of PPNG infections remains low, and provided very close supervision of the newborn babies' eyes is possible, it is still acceptable to initiate therapy with penicillin. These conditions are not met within developing countries. strict medical supervision is often impossible, and the prevalence of PPNG strains among circulating gonococci is above 20% in most countries. In Rwanda 52% of gonococcal isolates are PPNG strains, and of the non-PPNG strains 26% are chromosomally resistant to penicillin.[9]

Penicillin treatment is inappropriate in such circumstances, and if one wants to prevent blindness as a complication of gonococcal ophthalmia neonatorum highly effective antibiotic treatment has to be instituted from the start.

Treatment by a single dose presents a great advantage over multidose schedules, as does a regimen without eye ointment or drops. Local therapy to the eyes of the newborn is difficult in poor conditions, has low compliance, and may itself cause infections.

Single-dose intramuscular kanamycin if combined with a topical antibiotic for three days has been shown to be effective in gonococcal ophthalmia neonatorum due to PPNG and non-PPNG strains.[4,5] But although ototoxicity is unlikely with single-dose kanamycin therapy the potential for it makes it difficult to recommend the regimen as a first choice. Cefotaxime or gentamicin has been recommended for gonococcal ophthalmia neonatorum due to PPNG.[8] A case report showed that cefotaxime 100 mg/kg/day for seven days was effective.[2] As the third generation cephalosporins were shown to be highly effective in single-dose treatment of gonococcal infections in adults,[10,11] their effectiveness in gonococcal ophthalmia neonatorum could be expected. A single intramuscular dose of 125 mg of ceftriaxone was reported to have been effective in seven cases,[3] and the present study shows excellent results with a single-dose of cefotaxime.

A working group of the World Health Organisation recommended the addition of tetracycline ointment 1% for 10 days to a single intramuscular injection of 100 mg/kg of cefotaxime.[12] Our study proves that additional topical antibiotherapy is not required. Lower doses of cefotaxime, for instance a single intramuscular injection of 50 mg/kg, are probably as effective and should be studied further.

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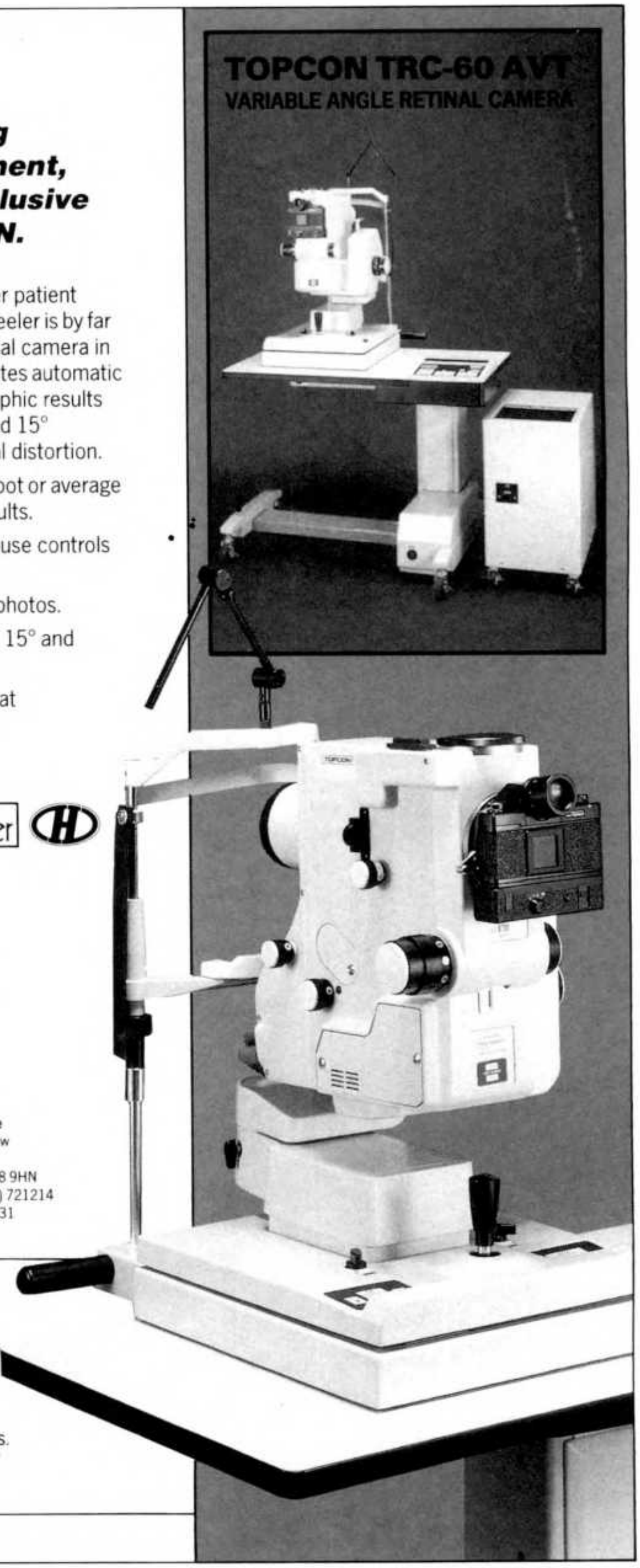

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Intravenous and intraocular ganciclovir for CMV retinitis in patients with AIDS or chemotherapeutic immunosuppression

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SUMMARY The efficacy and toxicity of ganciclovir given by intravenous or intravenous plus intravitreal injection were studied in nine patients with cytomegalovirus (CMV) retinitis; seven with AIDS and two with drug induced immunodeficiency. Five patients had retinitis with macular involvement in six sighted eyes; six patients had only peripheral retinitis in seven eyes. In two patients (two eyes) with macular involvement intravenous plus intravitreal injection of ganciclovir preserved sight; intravenous infusion alone did not in four eyes of three other patients. In seven eyes (six patients) with peripheral retinitis vision was retained regardless of the route of ganciclovir treatment. Following intravenous ganciclovir drug levels in the vitreous fluid were 1·4–2·2 mmol/l, that is, 44 and 65% of the concomitant serum concentration. Clinically and at necropsy three eyes showed no evidence of toxicity from intravitreal injection of ganciclovir. All of five patients with AIDS who received intravenous ganciclovir for more than one week developed leucopenia. CMV retinitis of the macula may be benefited with minimal drug toxicity by intravitreal injection of ganciclovir. Treatment of peripheral CMV retinitis in patients with AIDS may be optional.

Necrotising retinitis caused by cytomegalovirus (CMV) is one of the serious manifestations of immune deficiency states.[1,2] It has the potential for producing blindness and seriously depreciating the quality of life. In patients immunosuppressed by medication CMV retinitis can be controlled by withdrawal of the immunosuppressive drugs. In patients with the acquired immune deficiency syndrome (AIDS) the irreversibility of the immune suppression makes progression of CMV retinitis the expected course The increasing prevalence of AIDS and of chemotherapy causing immunosuppression has increased the occurrence of CMV retinitis and emphasised the need for effective treatment.[3,4]

The most effective antiviral drug for the treatment of CMV infections is 9-(1,3 dihydroxy 2-propoxymethyl) guanine (ganciclovir).[5-10] Its use offers the potential for stabilising and reversing CMV retinitis; however, it does not cure the disease. The requirement for long-term intravenous therapy often produces haematopoietic suppression. Treatment to prevent blindness has shown some benefit by funduscopy and visual acuity as measures of the effect In the absence of controlled comparative data a continuing critical appraisal of experience with ganciclovir treatment is necessary to judge its benefit, pharmacological requirements, toxicity, and the therapeutic options.

Material and methods

The diagnosis of CMV retinitis was based on the characteristic findings on funduscopic examination, absence of another explanation of the retinitis, and cultures for CMV. Cultures of peripheral blood leucocytes, throat secretions, and urine were made before treatment, and at approximately monthly

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intervals when prolonged treatment was given. The investigational protocol was approved by the Institutional Review Board for research involving humans, and informed consent was obtained from the patients. Patients were admitted to hospital for two weeks' initial treatment. Ganciclovir 2·5 mg/kg was given intravenously every 8 hours (except that one patient received 5 mg/kg). If the dose was tolerated without haemosuppression, a single daily dose was continued for 14–20 days. If the leucocyte count decreased below 1×10^9/l or by more than 50% of the initial count, further doses were deferred until reversal of the condition, and then ganciclovir was started again. After the initial course the treatment was continued, usually at home, with doses of 2·5 mg/kg daily on five days of the week.

Ophthalmic examinations were performed by the same ophthalmologist (JP) at least twice weekly before and during the initial treatment and frequently thereafter. The visual acuity was graded by the Snellen test and by standard terms for gross impairment· ability to count fingers, discern hand motion, and perceive light. Photographs of the retina were taken before and during treatment to record perceived changes. The response to therapy was rated as improvement, stabilisation, or progression.

In three patients blood samples were drawn at frequent intervals following infusion of 5 mg/kg or 2·5 mg/kg for measurements of the plasma drug level Instillation of intravitreal ganciclovir was done in the outpatient operating room by transcleral injection under direct visualisation. After removal of 0·1–0·2 ml of vitreous fluid, 200–400 μg of ganciclovir in 0·1 ml sterile water was injected. The procedure was performed two hours after the completion of the intravenous infusion of a dose of ganciclovir, and a simultaneous sample of serum was obtained.

Results

Of nine patients with necrotising CMV retinitis seven had AIDS and two were immunosuppressed for maintenance of a renal homograft. All of them had bilateral CMV retinitis. CMV was isolated from at least one clinical specimen from all but two patients. For the evaluation of treatment the patients were categorised according to macular involvement or only peripheral retinitis. The data are presented in Table 1.

MACULAR RETINITIS

Of five patients with necrotising retinitis involving the macula three were treated with intravenous ganciclovir and became totally or nearly totally blind during or shortly after treatment. One patient received the drug for only two days and withdrew because of fear of drug toxicity He became totally blind within a few weeks. Another patient progressed to total blindness during the first week of treatment, which was then discontinued A third patient had small areas of retinitis involving the macula bilaterally. Initially the visual acuity was good, 20/20, but on a regular schedule of treatment with intravenous ganciclovir (2·5 mg/kg five times a week) over a period of 43 days until death vision deteriorated progressively to 20/70 (OS) and to perceiving hand motion (OD)

In two eyes of two patients with macular retinitis ganciclovir was given by intraocular injection as well as by intravenous infusion. Following the intravitreal injection the retinal lesions improved in each of the eyes as judged by funduscopy and by visual acuity. One patient's visual acuity of counting fingers at 5 feet (CF 5) (1·5 m) was improved to 20/40 and retained for one month after the intravitreal injection until death occurred from other causes. The other patient's visual acuity deteriorated from 20/100 to CF 5 with intravenous therapy alone, but was improved to 20/200 and retained for approximately two months after the intraocular injection of ganciclovir; in the third month vision deteriorated while the patient was receiving intravenous doses of ganciclovir intermittently owing to toxicity.

PERIPHERAL RETINITIS

In seven eyes of six patients CMV retinitis involved only the peripheral retina. In all of them visual acuity was good (20/20 and 20/40), and it remained so until the time of death regardless of whether the treatment regimen included intraocular treatment or only intravenous therapy. Four patients with AIDS died within one to six months In two patients with renal allografts ganciclovir was given only intravenously and the dose of immunosuppressive drugs reduced. The retinitis healed and remained quiescent without further treatment for eight months and one month respectively.

PHARMACOLOGY AND TOXICOLOGY

Intravenous infusion of 2·5 mg/kg of ganciclovir produced peak serum levels of 11 to 19·4 mmol/l; 5 mg/kg in one patient gave a peak level of 25·6 mmol/l. Trough levels after eight hours were 1 mmol/l or less. Two hours after intravenous infusion ganciclovir levels in the vitreous fluid were approximately one-half the concentration in serum. Concomitant serum and vitreous fluid concentrations of ganciclovir in two eyes of two patients are given in Table 2. Based on a distribution volume of 11·7 ml[11] the calculated drug levels after intraocular injections of 200, 300, and 400 μg of ganciclovir were initially approximately 70, 105, and 140 mmol/l respectively. One month after

Table 1 *Necrotising CMV retinitis treated with ganciclovir*

Patient data	*Patients with macular involvement*					*Patients with peripheral disease*			
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Treatment·	*Intravenous only*			*Intraocular*		*Intravenous only*			
Age, yr	30	42	30	28	44	28	30	42	44
Sex	Male	Male	Male	Male	Male	Female	Male	Female	Female
IV dose (g)	0·8	5·4	9·2	8·9	9·9	5·4	3·6	5·8	5·5
Duration, days	2	6	53	90	30	15	8	14	20
Retinal involvement[a]									
Before treatment									
OS	M	Old	M	P	M	P	P	Old	P
OD	M	M	M	M	P	ON	P	P	Old
After treatment									
OS	NC	NC	↓	NC*	↑*	↓	↑	NC	↑
OD	NC	↓	↓	↓/↑*	↑	↓	↑	↑	NC
Visual acuity[b]									
Before treatment									
OS	NLP	NLP	*20/20	20/20	CF5	20/20	20/30	CF5	20/20
OD	20/200	CF5	20/20	20/100	20/20	NLP	20/40	20/20	CF5
After treatment									
OS	NLP	NLP	20/70	20/20*	20/40*	20/20	20/30	CF5	20/20
OD	20/200	NLP	HM	CF5 20/200*	20/20	NLP	20/40	20/20	CF5
Viral cultures[c]									
Before treatment									
Blood	NA	+	−	−	−	−	−	−	−
Urine	NA	−	+	+	+	−	+	+	−
Throat	NA	+	−	+	+	+	+	−	−
After treatment									
Blood	NA	−	+	−	−	−	−	−	−
Urine	NA	−	+	−	−	−	+	−	−
Throat	NA	NA	+	−	−	−	−	−	−
Leucopenia									
$<1\times10^9$/l/>50% fall	No	No	Yes	Yes	Yes	Yes	Yes	No	No

[a] M=macular lesion, P=peripheral retina, ON=optic nerve, *=200–400 µg intraocularly, NC=no change, ↓ =progression of lesion(s), ↑ =improvement of lesion(s) [b] NLP=no light perception, CF5=count fingers at 5 feet (1·5 m), HM=perceive hand motion
[c] NA=not available

intraocular injection and continuing intravenous doses, the inoculated eye of one patient had a slightly higher concentration of drug than the opposite eye.

In one patient CMV viraemia in the leucocyte buffy coat persisted, though peak ganciclovir serum levels of 19·4 uM/ml were attained. In all other patients viral cultures for CMV were rarely positive during the period when ganciclovir was given.

Of seven patients with AIDS and an initial leucocyte count of $>1\times10^9$/l five received ganciclovir for more than one week and all of them developed leucopenia. In four the granulocyte count decreased to less than 1×10^9/l and in the other decreased more than 50%. All seven patients with AIDS died. One patient had reactivated *Pneumocystis carinii* pneumonia and also CMV pneumonia, another had CMV pneumonia with probable disseminated CMV; two other patients had overtly disseminated CMV infection.

CMV retinitis was confirmed in six eyes enucleated from three patients at necropsy, including three injected with ganciclovir. Virus was recovered from the retina of one eye. In none of the patients could another infection of the retina be identified histologically or by cultures for viruses and bacteria. The three eyes that were injected with ganciclovir showed no gross or microscopic evidence of drug toxicity.

Discussion

With a disease as potentially devastating but as variable as necrotising CMV retinitis, and a drug with the potential efficacy and toxicity of ganciclovir, controlled trials would be important but possibly unethical. The experience presented here, as in other reports, is limited and without controls on which to base firm conclusions. In the absence of such investigation it is important to develop criteria for selection of patients and expectations from treatment with ganciclovir. A fundamental question is whether all patients with necrotising CMV retinitis will benefit from ganciclovir treatment. In patients with AIDS,

Table 2 *Levels of ganciclovir in serum and vitreous fluid, mmol/l*

Patient no	*Duration of treatment 2·5 mg/kg 8 hourly*	*Time after infusion*	*Serum (peak/trough)*	*Vitreous*	*Ratio V/S*
4	Initial	2 h*	3·2	1·4 OD	44%
5	4 days	2 h*	3·4 (11·0–1·5)	2·2 OS	65%
	30 days	36 h (necropsy)	ND	1·4 OS 0·9 OD	

ND=not done *Intravitreal injection

cure of CMV retinitis with ganciclovir cannot be achieved. In its place the preservation of adequate vision might be a suitable aim. When CMV retinitis is only at a peripheral focus, the rate of progression to blindness may be slow and in patients with AIDS may be preceded by death. For those with initial involvement of the macula, intravenous treatment appears to be inadequate to save their sight. The anatomical differentiation of macular and non-macular involvement of the retina might serve as a basis for the categorisation of patients for different treatment regimens.

When the retinitis does not impair visual acuity, the avoidance of drug toxicity may be preferable to the expected gain when long-term intravenous ganciclovir is required. The levels of ganciclovir in vitreous fluid following intravenous administration of the recommended dose (2·5 mg/kg) may reach 50% of the concomitant serum concentration, but are probably inadequate for effective antiviral action against more than a third of the strains of CMV[5] Direct intravitreous injection of ganciclovir appears to be non-toxic and can produce inhibitory levels of drug at the site of infection for many hours.[11–14] When given in conjunction with intravenous therapy, the preservation of an inhibitory drug level in the eye may be present for a relatively long period. During that period CMV can be suppressed, the lesions stabilised, and vision preserved or improved. One patient has received multiple injections.[11] The optimal and safe time intervals to repeat the intravitreal injections, if necessary to maintain the suppressive effect, are not known and may vary among patients. If acceptable, infrequent intravitreal injections could be programmed by clinical and funduscopic signs to fit the need

The best regimen for maximum benefit and minimal drug toxicity remains unproved. Our experience suggests that ganciclovir therapy of peripheral retinal lesions can be individualised and observation without specific treatment justified. When macular lesions are initially present, intravitreal injection of ganciclovir may give the greatest likelihood of preserving sight with minimal drug toxicity.

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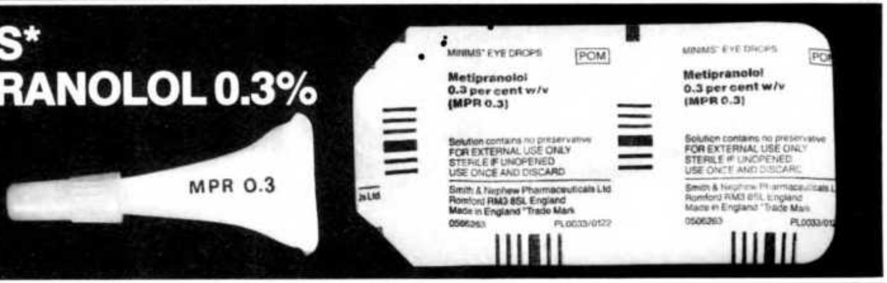

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British Journal of Ophthalmology, 1988, **72**, 525–529

Treatment of cytomegalovirus retinitis with ganciclovir (9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine (BW B759U))

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SUMMARY Six patients (11 eyes) with virologically confirmed cytomegalovirus (CMV) retinitis involving the posterior pole of the eye were treated with a new drug, ganciclovir. Treatment with intravenous ganciclovir consistently halted progression of retinitis and produced improvement in measures of visual function. However, within three weeks after cessation of therapy renewed CMV activity and worsening of visual function were observed in most cases. Maintenance therapy with ganciclovir extended the period of remission from CMV retinitis.

The acquired immunodeficiency syndrome (AIDS) is an epidemic disorder characterised by immunological impairment that predisposes to the development of cancer and to life threatening infections with opportunistic organisms. The syndrome, first reported in homosexual men, and subsequently in intravenous drug abusers, recent Haitian immigrants, haemophiliacs, transfusion recipients, and infants of women in known risk groups for AIDS, has been well documented since 1981.[1-3] Opportunistic infections including *Pneumocystis carinii* pneumonia, oral and oesophageal candidiasis, herpes simplex, herpes zoster, cytomegalovirus, systemic cryptococcus, atypical mycobacterial infections, and toxoplasmosis as well as Kaposi's sarcoma and non-Hodgkin's lymphoma are frequently seen in these patients.[1-7]

Cytomegalovirus (CMV), a common and often severe opportunistic infection in these patients, may be present in the retina in the absence of clinically apparent cytomegalovirus infection elsewhere The retinal manifestations of CMV are retinal necrosis with haemorrhages, exudates, retinal vasculitis, and a slow but steady progression to complete retinal destruction.[8-10]

There is no efficacious treatment for either ocular or systemic cytomegalovirus infections. A new experimental intravenous drug, ganciclovir (BW B759U or (9-[2-hydroxy-1-(hydroxy-methyl) ethoxymethyl] guanine), an analogue of acyclovir, is being evaluated for the treatment of patients with CMV retinitis. This report describes an initial series of patients with AIDS and CMV retinitis who have received this new agent.

Materials and methods

The cases reported are the first six patients (11 eyes) with AIDS and CMV retinitis who consented to treatment at the Beth Israel Medical Center (BIMC) with the drug ganciclovir The patients included five men and one woman, ranging in age from 29–55, and all with history of homosexuality or intravenous drug abuse and a diagnosis of AIDS. All patients had positive urine cultures for CMV as well as increased serological titres for CMV. At the start of treatment their visual acuities ranged from 20/30 to no light perception (Table 1). All patients had disease involving the posterior pole, that is, involvement of either or both the macula and optic nerve.

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Table 1 *Visual acuity after 21 days of therapy*

Patient	*Before therapy*	*After therapy*
1	LP with projection OS	20/300 OS
2	20/30 OD	NLP OD
	20/30 OS	NLP OS
3	20/50 OS	20/30 OS
	CF at 2·4 m OD	20/200 OD
4	NLP OD	NLP OD
	20/50 OS	20/50 OS
5	20/100 OD	20/70 OD
	HM OS	HM OS
	CF at 2·4m OD	20/30 OD
6	20/30 OS	20/30 OS

NPL = no light perception. LP = light perception. CF = counting fingers. HM = hand motions.

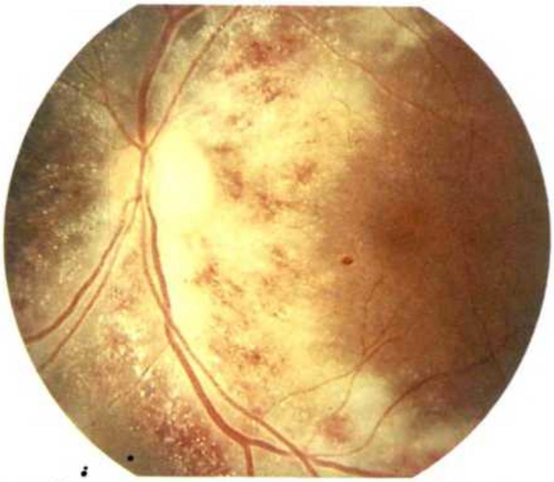

Fig. 2 *After 21 days of therapy both the optic nerve and arcades are clearly visible. The acuity was stable at 20/30.*

Complete blood counts including platelet counts, blood chemistries including liver function tests, electrolytes, blood urea nitrogen, and serum creatinine were obtained prior to initiating treatment and followed up at least every three days during therapy. In two patients on maintenance therapy these tests were performed once each week.

A complete ophthalmological examination was performed which included visual acuity testing, external and slit-lamp examination, intraocular pressure determination, and funduscopic evaluation. A baseline fluorescein angiogram, electroretinogram, and visual evoked reponse were performed on all patients. All patients received a baseline macular function test by the macula program of the Humphrey automated perimeter.

While in the hospital the patients had daily eye examinations, with fundus photography performed every third day. Macular function tests were repeated at least weekly, and fluorescein angiograms were repeated on a weekly basis.

All patients received ganciclovir 2·5 mg/kg intravenously every eight hours for a 21-day course. Two patients received more than one course in hospital. Two of the patients received subsequent maintenance therapy after finishing the 21-day course. It consisted of 5 mg/kg intravenously once per day for

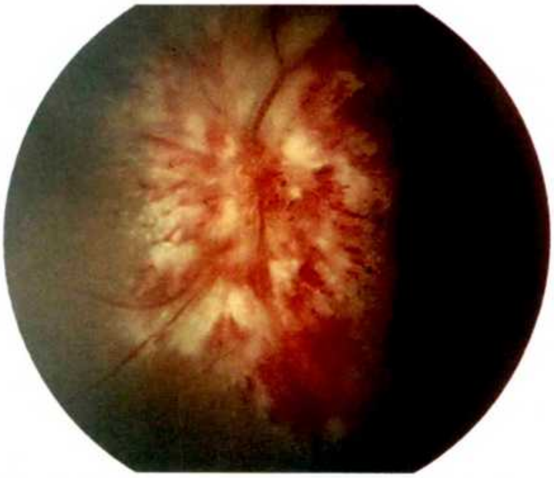

Fig. 1 *Case 3. There is extensive involvement of the optic nerve head with obscuration of the disc. The visual acuity in this patient was 20/50.*

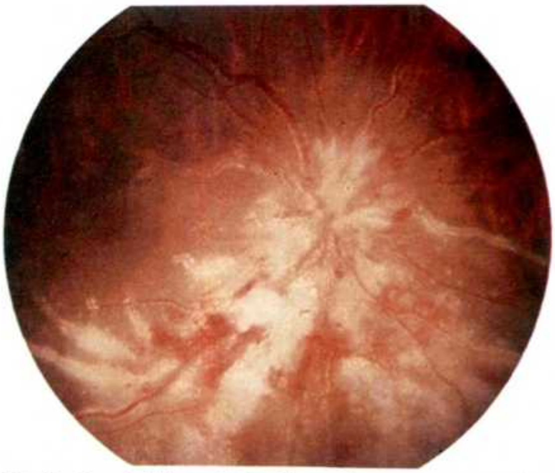

Fig. 3 *Case 6. The patient's right eye demonstrates extensive involvement of the optic nerve head as well as the sheathing of the arteries and veins. There are some obliterated arteries inferior to the disc. There is extensive oedema throughout the posterior pole. The visual acuity was counting fingers at 2·4 m.*

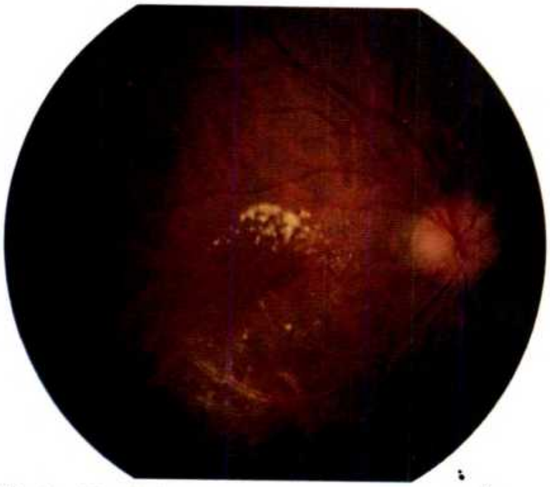

Fig. 4 *After 10 days of therapy there is still some mild residual oedema of macula, and some borders of the optic nerve are now clearly visible. The acuity was 20/200.*

five of seven days every week administered through a Broviac catheter placed into a subclavian vessel.

Results

We found that six of 11 eyes (54·5%) improved their visual acuity by at least one line on the Snellen chart by the end of the 21-day course (Table 1, Figs. 1–5). Three eyes (27·2%) remained stable at pretherapy acuities and two eyes (18·1%) deteriorated. Patient 2 had both bilateral progressive scarring of the posterior pole and optic atrophy, resulting in a final visual acuity of no light perception. Thus ganciclovir improved or stabilised 81·7% of treated eyes. Two patients relapsed and required subsequent therapy more than once and lost an additional line of acuity on the Snellen chart; however, their final acuities remained better than their pretherapy acuities.

All patients had a drop in their white blood cell counts. In one case the dose of ganciclovir was decreased to 1 mg/kg intravenously every eight hours while the patient remained absolutely neutropenic (less than 1×10^9 white cells/l), and in another case the drug was terminated. The liver function values increased in five of the six patients; however, this did not interfere with the therapy regimen. Three of the six patients died after therapy, one from toxoplasmosis and two from disseminated CMV. One was lost to follow-up. These patients had not received maintenance therapy because they refused any further medications. One patient died from septicaemia while on maintenance therapy.

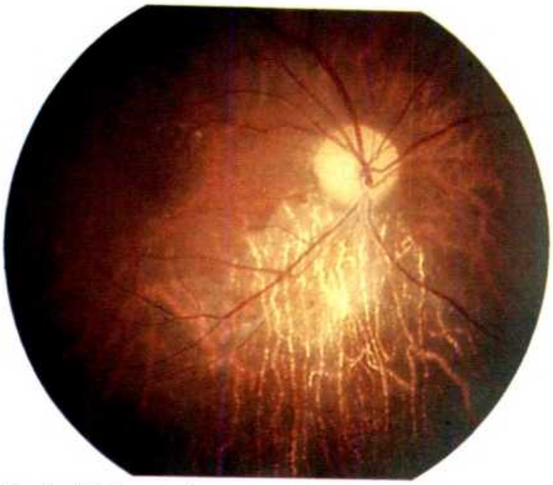

Fig. 5 *While on maintenance therapy the fundus significantly cleared. The visual acuity progressed to 20/30 in the right eye. The patient reported a great sense of wellbeing while on maintenance therapy.*

Discussion

Active CMV infection can be diagnosed by an increase in complement fixation antibodies, culture of the virus in serum, urine, saliva, or other body fluids, or biopsy confirmation of cells showing the classic histopathological picture. In the eye the virus has been isolated from tears[11] or conjunctiva[12] of patients with and without retinitis and does not correlate well with ocular symptoms. In patients with retinitis cultures of subretinal fluid and vitreous may be positive.[13–16] In patients with panuveitis aqueous taps have yielded live virus.[15 17] On occasion the diagnosis can be made by a vitreous tap and culture.[9 10] CMV retinitis has been found in 15% to 46% of AIDS patients in most series from the United States.[18–22] Once observed in these patients, the retinitis tends to be slowly but inexorably progressive, often affecting both eyes and ultimately causing complete blindness.

Therapy for cytomegalovirus retinitis has been for the most part unsuccessful. Limited experiences with transfer factor[23] and antiviral drugs such as adenine arabinoside,[24] floxacidine, and acyclovir have yielded only an occasional report of success.[25–27] Clinically treatment with ganciclovir also did not appear to provide a permanent cure in the present series. Although this agent consistently halted the progression of the retinitis several days after initiation, and improved both the vision and the retina, these effects were maintained only during therapy and for a short time after drug therapy was withdrawn.[28–33] Approximately three weeks after completion of a typical 21-day course, renewed CMV activity was observed in the retinas of cases 1, 2, 4, and 5.

Ganciclovir or BW B759U is an acyclic nucleoside analog of acyclovir. It is active against herpes simplex types I and II (HSV), varicella zoster virus (V2V), Epstein-Barr virus (EBV), and human cytomegalovirus (HCMV) In studies on human cytomegalovirus of strain AD169, BW B759U did not appear to affect virus early gene function. However, the synthesis of several late structural proteins was inhibited.[34] It appears that ganciclovir is incorporated by intranucleotide linkage into the DNA extracted from HSV infected cells. This suggests that it does not function as a chain terminator as does acyclovir. Ganciclovir strongly inhibits the synthesis of viral DNA in human cytomegalovirus infected cells as well as in herpes simplex virus infected cells.[23 35] In essence this new drug is phosphorylated and eventually functions as an alternative substrate, as a competitive inhibitor of the human cytomegalovirus induced DNA polymerase.

The main toxic effects of ganciclovir include reversible bone marrow depression and irreversible testicular atrophy Assays done on the drug show that the toxicity falls between that of vidarabine and that of acyclovir. However, in patients with AIDS, HTLV-III/LAV virus also produces cytopenias and may synergistically act to decrease the white blood cell count, complicating evaluation of drug toxicity in these patients. Drug toxicity is believed to be minimal at 2·5 mg/kg. At a dose of 5 mg/kg bone marrow suppression may occur At a dosage of 7 mg/kg per day in animal models testicular atrophy occurred.[36] At dosages of 20 mg/kg per day diarrhoea and emesis occurred in addition to cytostatic effects (bone marrow, thymus, lymphoid organs) and testicular atrophy. At large doses of 60 mg/kg per day animals experienced diarrhoea and emesis, cytostatic effects, testicular atrophy, maturation arrest of gastrointestinal cells, and death.

In the early patients reported here, no side effects were noted other than a decrease in the white blood cell count. In most patients it decreased slightly, and in two the treatment was reduced or stopped until the white blood cell count returned to normal. One case (3) experienced a transient decrease in the white blood cell count several days after finishing a first 10-day course of therapy. It could not be determined, however, whether this represented a delayed effect of the ganciclovir therapy or a consequence of other concurrent medications, the direct effect of the CMV itself, or the underlying immune deficiency. More interesting was that many of these patients stated they had an improved feeling of general wellbeing while on the drug. Those patients who had headaches noted improvement while on therapy. One can theorise that the medication may be able to enter the central nervous system and inhibit the virus despite animal studies suggesting poor CNS penetration.

Ganciclovir appears to slow or halt progression of CMV retinitis and allow for healing and visual improvement as shown by fundus photographs and macular fields. However, after therapy is discontinued the retinitis recurs, usually within three weeks. In addition recurrent episodes of CMV retinitis appear to respond more slowly and incompletely to treatment than do the initial episodes. As a result of the experience we report here, patients are being put on a maintenance schedule of 5 mg/kg intravenously in one dose, five times a week, after the initial course of therapy is completed. It is hoped that such a regimen will prevent recurrent retinitis.

The authors express their thanks to Burroughs Wellcome Company for providing them with the drug BW B759U

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Severe herpetic keratitis. I: Prevalence of visual impairment in a clinic population

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SUMMARY We report a prevalence study of the best visual acuity in the affected eye of 100 selected patients with herpetic keratitis seen during a two-year period. Sixty-two patients retained an acuity of 6/9 or better without requiring penetrating keratoplasty (PK). The prevalence of reduced visual acuity severe enough to warrant PK was 33%. Patients requiring PK for whom full clinical records were available suffered a mean of 6·8 episodes of keratitis. In this group of patients the vision of 18 fell from 6/6 to 6/60 over a mean period of 8·5 years. Once visual acuity was permanently reduced to 6/12, 78% of patients proceeded to lose vision to 6/60. Unilateral visual impairment occurs in at least a third of patients with severe herpetic keratitis. Once vision falls permanently to 6/12, the long-term prognosis for vision appears to be poor.

Bristol Eye Hospital provides ophthalmic care for the City of Bristol and surrounding areas, a population of approximately 863 000. The Corneal Clinic has been established for 14 years, and all cases of severe herpetic eye disease are referred here. However, it should be noted that simple epithelial disease which heals readily with little or no visual loss is not routinely seen in this clinic.

We have surveyed the population with herpetic keratitis seen in the Corneal Clinic and recorded the best corrected visual acuities (VA). When penetrating keratoplasty was required, best VA prior to PK was recorded.

We wished to know what proportion of patients with severe herpetic keratitis lost significant VA, and we tried to ascertain how rapidly such loss occurred. To record rate of loss of VA we arbitrarily chose 6/12 and 6/60, and noted the time for eyes with acuities of 6/6 to fall to these levels. These levels were chosen because, if they had represented best visual acuity in the best eye, they would have prevented the patient from driving or would have allowed them to be registered as partially sighted. Since official statistics do not include unilateral loss of sight, and since the majority of herpetic eye disease is unilateral, such patients will not appear in these statistics.

In addition we have recorded the number of recurrences of herpetic keratitis associated with a reduction in VA severe enough to warrant PK.

Materials and methods

A computerised database of all patients seen in the Corneal Clinic was begun in August 1984. It was maintained on the University main-frame Multics computer with an XQX editor. Recorded data included all diagnoses and adequate information for retrieval of hospital notes. The database was augmented and updated on a weekly basis after each clinic, and thus patients were prospectively recruited into the database.

At the end of July 1985 the database was searched for all patients with herpetic keratitis. One hundred and four patients were identified. Case notes could be located for 100 of them, and these formed the study group. The group included new patients with active keratitis during the period August 1984 to end of July 1986, old patients with recurrent keratitis, old patients with quiescent disease attending for review, pre- and postoperative patients, and those seen some time after penetrating keratoplasty.

The characteristics recorded for each patient

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Table 1 *Patient characteristics recorded*

All patients
Sex
Age first seen with herpetic keratitis
History of previous attacks
Right or left or both eyes affected
Disease when first seen

Subpopulation with vision reduced to at least 6/12
Sex
Age first seen with herpetic keratitis
Time from onset to vision of 6/12

Subpopulation with vision reduced to at least 6/60
Sex
Age first seen with herpetic keratitis
Time from onset to vision of 6/60

Subpopulation undergoing penetrating keratoplasty (PK)
Sex
Visual acuity when listed
Number of recurrences prior to listing for PK
Age at time of PK
Initial disease
Number of outpatient visits and days as in patient during the year before and two years after PK

included age at onset and at various times thereafter, sex, and whether PK was required for visual rehabilitation. A full list of characteristics is shown in Table 1.

Results

There were 51 male patients and 49 females. The mean age at onset was 38·6 years for the 68 patients who had not been treated elsewhere prior to being seen in Bristol. The left eye was involved in 62 patients and the right eye in 38 ($p>0\cdot05$). Five patients had bilateral disease. The diagnosis of herpetic keratitis was clinical in all cases (100 patients), based on observation of a dendritic or geographical ulcer, or typical stromal disease.

The disease at presentation was epithelial (dendritic or geographical ulceration) in 41 patients, stromal in eight, and mixed in 51. At the time of the survey 62 patients had a VA of 6/9 or better after medical therapy. Five patients had acuities between 6/12 and 6/24. All 33 patients whose VA had fallen to 6/36 or worse had received a PK.

The presenting keratitis in those patients who required PK had been purely epithelial in 10 patients (30·3%), purely stromal in two patients (6·1%), and mixed stromal and epithelial in 21 patients (63·6%). Details on the number of recurrences of keratitis prior to PK were available for 20 patients (60%); these patients had a mean of 6·8 recorded recurrences (range 3–15) before requiring PK.

Of the 33 patients who required PK 11 had no recorded VA better than 6/60. These included patients refered to Bristol from elsewhere. However, 18 patients had clinical histories which recorded visual impairment from 6/6 to at least 6/60. There were 11 male patients and 7 female. The mean age at onset of herpetic keratitis was 51·0 years for male patients and 42·1 years for females. The mean time taken for vision to fall from 6/6 to 6/60 was 8·5 years.

In addition to the 18 patients who lost vision from 6/6 to 6/60 a further five lost vision to between 6/12 and 6/36. We were therefore able to note the rate of visual loss to 6/12 in 23 patients. These patients lost vision from 6/6 to 6/12 in a mean of 4·8 years. Of the 23 patients who permanently lost vision to 6/12 18 progressed to 6/60 or worse (78%).

Discussion

Herpes simplex virus (HSV) causes disease not only when it first infects the eye, but also by producing recurrent disease (reviewed by Falcon[1]). Recurrent disease is thought to occur when HSV, which has established latency in the trigeminal ganglion, is shed into corneal tissue via neural pathways. Recently latency (or persistence) of HSV in ocular tissue has been reported[2-6] (Claoué *et al.*, in preparation), and clearly this may play a part in the genesis of severe recurrent disease and chronic stromal keratitis.

The pathogenic mechanisms whereby HSV produces stromal scarring and visual loss are not known. However, laboratory studies have suggested a role for T-cell mediated pathogenesis,[7] and it is known that the cell population in corneal buttons removed for PK 'à chaud' contain a large proportion of cytotoxic T cells.[8,9]

The incidence of herpetic keratitis is estimated to be five patients per 10 000 population per year,[10] and 46% retain a visual acuity of 6/6 over a period of seven years.[11] Thus 54% had reduced vision and could be considered to have severe disease, including 17% whose vision fell to 6/18 or worse. While we do not have a precise figure for the total number of new patients with herpetic keratitis seen during the two-year period studied at this hospital (serving a population of 863 000), it is known that approximately 120 new patients with herpetic keratitis are seen per year.[12] This is less than that predicted from the experience of Norn.[10]

As in previous studies (reviewed by Tullo[13]) we find that the onset of disease is predominantly in the fifth decade of life. However, the male preponderance reported by other authors[10,14-17] was not found. This could be due to a number of factors, including a reduced frequency of severe disease in males. A number of other authors have also failed to find an obvious male preponderance among patients with stromal disease[18,19] or keratouveitis,[20,21] and we believe that our patients are similar to those seen elsewhere in the United Kingdom.

It is generally known that patients with herpetic keratitis may lose vision, though this particular aspect has not been extensively studied. There is no mention of the extent of visual loss in herpetic eye disease either in ophthalmic reference texts[22 23] or in specialist texts on herpetic eye disease.[24] This is in part because of the problems of following up patients for the prolonged periods required to detect visual loss, a point first made by Thygeson *et al.*[25] in 1956. However, 17% of patients in one series had vision reduced to 6/18 or worse[11] and 23.4% of patients in another series lost vision to at least 6/12.[26] In a series of 15 patients with herpetic keratouveitis 40% had a visual acuity of 6/12 or worse.[16] The prognosis for patients with disciform keratitis seems to be even worse, with 30% having visual acuities of 6/60 or worse at presentation, of whom the majority (67·5%) had the same or worse vision after treatment.[19] These studies were performed by different methods from those reported here, and are also in genetically different populations. Thus it may be difficult to compare the results of other workers directly with our own.

Although we found that 33% of our patients developed visual acuities of 6/36 or worse, other patients in our study group may go on to develop visual impairment, and so this figure can represent only a minimum.

The majority of patients in this study presented originally with either purely epithelial disease or mixed epithelial and stromal disease (often a small infiltrate under an ulcer). Despite treatment many progressed to significant loss of vision. However, this treatment was not standardised, and it is possible that the latest penetrating antiviral drugs such as acyclovir may prevent progression to visual impairment or alter the recurrence rate.

Those patients who regained good vision after their initial episode were observed to lose vision to 6/12 in 4·8 years, and to 6/60 after 8·5 years despite treatment, though therapy was not identical for all the patients. The patients with loss of vision to 6/60 were on average older when first seen than the less severely affected group. It is known that stromal keratitis is commoner with increasing age.[27]

The finding that 33% of patients with severe herpetic keratitis require PK stresses that visual loss is frequently severe. Since these patients regained good vision and did not require simultaneous or early cataract surgery, it is reasonable to attribute the visual loss exclusively to the keratitis. Moreover, since the visual loss is most often unilateral, official statistics of blindness will not show the incidence, as they are based on the best vision in the better eye. The number of episodes of keratitis producing a degree of handicap requiring keratoplasty can be as little as 3, while the mean is only 7, stressing the need for optimal therapy each time a recurrence occurs. It is, however, worrying to note that 78% of patients who permanently lost vision to 6/12 later progressed to 6/60 or worse, suggesting that even quite mild degrees of visual loss in patients with herpetic keratitis should be considered as serious indicators of prognosis. Since this is not a closed study, the figure of 78% can be regarded as only a minimum. There is thus a clear need for optimal medical therapy for patients with severe herpetic keratitis.

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Pattern visual evoked potentials in hyperthyroidism

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SUMMARY Pattern reversal visual evoked potentials (VEPs) have been elicited in 16 female hyperthyroid patients before and after treatment and compared with those from a similar group of age and sex matched control subjects. No effect on latency was seen, and although larger amplitude values were noted in the thyrotoxic group these too were not significant. We would conclude that hyperthyroidism per se has little effect on the pattern reversal VEP, and any observed effect on these potentials is probably due to other factors.

Thyroid disease is a known cause of nervous system dysfunction. Hypothyroidism has been reported to affect both the electroencephalogram (EEG)[1] and the visual evoked potential (VEP) to flash stimulation, the feature of note in the latter being a delay in conduction.[2] In more recent studies utilising the VEP to pattern stimulation this observed delay was shown to show reversibility after appropriate treatment.[3 4] While hyperthyroidism has been shown to produce a so-called 'fast' rhythm EEG[5] (a feature which was observed to disappear when the patients became clinically euthyroid), to our knowledge only one study has investigated VEPs in hyperthyroidism[6] and this adopted flash stimulation. No effect on latency was observed, though larger amplitudes were noted.

It is obviously important to be aware of any abnormalities in the VEP that are due to hyperthyroidism if electrodiagnostic techniques are to be used in the treatment of any optic nerve disease which may result from such thyroid dysfunction. The intention of this study therefore was to investigate the pattern VEP in hyperthyroid patients before and after treatment and to compare the results with an appropriately matched group of control subjects.

Patients and methods

Sixteen hyperthyroid patients (mean age and SD= 38·3 and 7·2 yr), all female, and with biochemically proved (untreated) thyrotoxicosis, were recruited from the endocrine clinic. Patients with eye disease unrelated to thyroid disease or receiving drug therapy which could influence the VEP were excluded. All patients had a full ophthalmic assessment which consisted of measurement of corrected visual acuity, biomicroscopy, tonometry, funduscopy, exophthalmometry, and assessment of ocular motility and visual fields. Apart from the results of exophthalmometry and ocular motility assessment the patients were found to be normal. Most of the group had mild thyroid eye disease consisting of slight proptosis and lid retraction. Two patients developed extraocular muscle involvement during the study; however, there were no cases of corneal ulceration or optic nerve compression. VEP investigations were performed on patients in the thyrotoxic state and then repeated at least six months after they had been rendered euthyroid. Control of the disease was medical (nine cases), surgical (three cases), and by radioactive iodine (four cases).

The control group comprised 16 female subjects who were age matched to the patient group not only with respect to mean and standard deviation (37·6±10·5 yr) but also in the distribution of ages. They were selected on the criterion that they were ophthalmologically normal in all respects.

ELECTROPHYSIOLOGY

The checkerboard stimulus was produced by a video pattern generator on a high quality TV monitor. Luminance modulation of the pattern was selected to give the pattern reversal mode of stimulation at a rate of 2 per second. The checksize of the stimulus was 50′

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and the visual field subtended, 17°×14°. The overall luminance of the TV screen—with and without pattern—was maintained constant at 10·4 Cd M^{-2}. Pattern contrast (defined as $(L_{max}-L_{min})/(L_{max}+L_{min})$ where L_{max} and L_{min} are the luminance of the bright and dark checks respectively) was adjusted to be 95%.

Silver/silver chloride disc electrodes were attached to the scalp with collodion in the following positions as defined by Jasper[7]. active—Oz, reference—Cz, earth—Pz. A Medelec electrophysiological recording unit was used to amplify, average, and store the evoked potentials The amplifier band width was 0·8–80 Hz, and either 64 or 128 epochs of 300 ms duration were averaged depending on the size of the response. Two averages were obtained under each stimulus condition to check for consistency, and quantitative analysis was performed on the average of these two. The patients were given short periods of rest between each separate measurement so as to minimise fatigue and any concomitant increase in response variability. With respect to latency, the P100 component was analysed, and for amplitude a peak-peak measure between components P100-N150 was adopted. A permanent record of the responses was made on an X-Y plotter.

Monocular stimulation was adopted in all investigations, the subject being instructed to maintain fixation and focus on a small LED marker attached to the centre of the screen. This was monitored during the investigation by closed circuit TV

Prior to the commencement of the test the subject was preadapted to the luminance of the blank screen for 5 minutes. This was the only source of illumination in an otherwise darkened room. The test was concluded with the measurement of the subject's pupil size under experimental conditions.

STATISTICS

In terms of absolute measurements of both latency and amplitude one value was selected for analysis at random from either the right or left eye in both control and patient groups. In addition, the magnitudes of interocular differences in latency and amplitude were also computed to facilitate comparison between distributions where interindividual differences in absolute values had been eliminated. Normal parametric distributions were assumed and therefore significance was determined by Student's *t* test. The level of significance chosen for the study was 1% ($p \leq 0.01$).

Results

Characteristic VEPs from the right and left eyes of a control subject are illustrated in Fig 1a. The main components of these responses, namely the P100 and N150, are clearly evident in both RE and LE tracings. In Figs 1b and 1c the VEPs elicited from a hyperthyroid patient before and after treatment are shown for comparison. There appeared to be little qualitative difference in the form of either set of responses, both in relation to each other or to those observed in the control subject. With respect to P100 latency, no overt differences were apparent, but amplitudes appeared to be somewhat larger in the responses from the patient than those from the control subject.

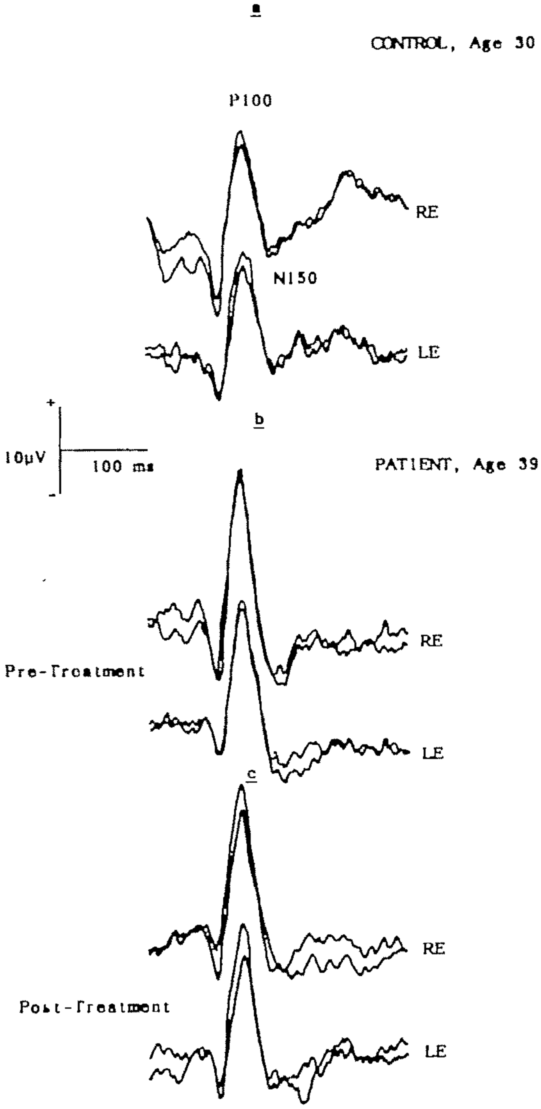

Fig 1 *VEPs from a control subject* (a) *and from a patient, before treatment* (b) *and after treatment* (c).

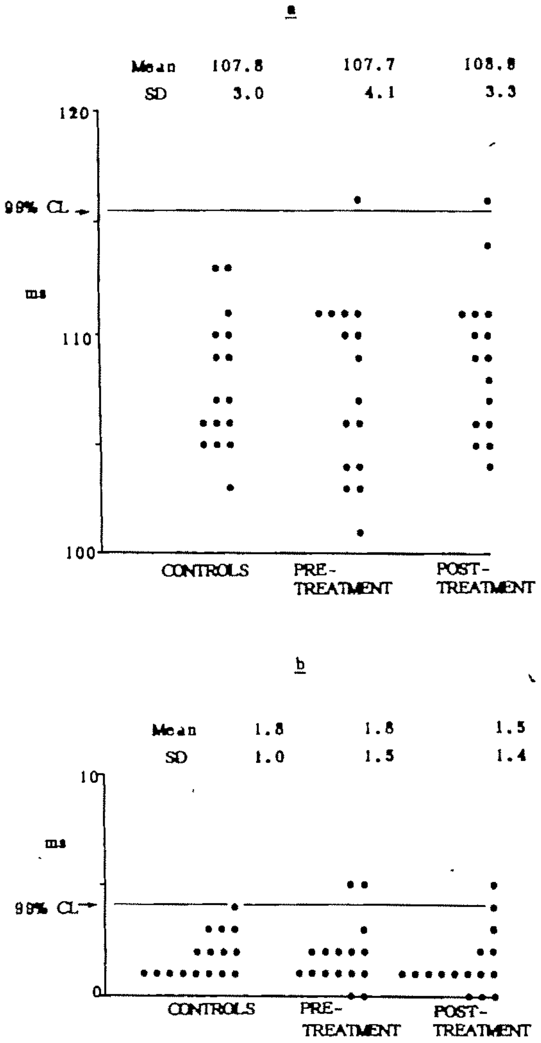

Fig. 2 *Scattergrams of absolute P100 latency* (a) *and interocular latency difference* (b) *in control and patient groups CL=confidence limit.*

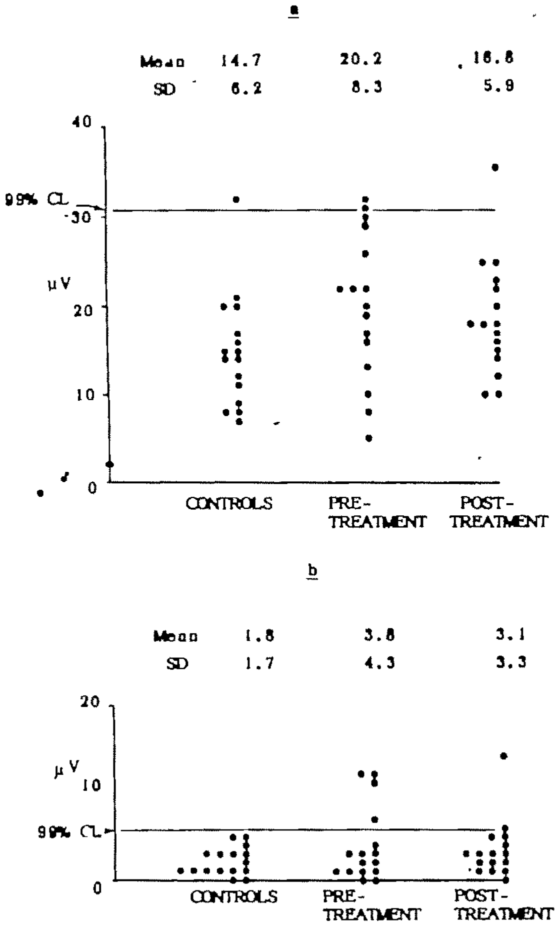

Fig 3 *Scattergrams of absolute P100 amplitude* (a) *and interocular latency difference* (b), *in control and patient groups. CL=confidence limit.*

When the entire control and patient group data were analysed the impressions gained from the previous two subjects were essentially found to be representative of the complete study. In Fig. 2a scattergrams of P100 latency in the control group and before and after treatment in the patient group are illustrated. No apparent difference in the separate distributions was evident, a feature confirmed when mean and standard deviations were calculated (these are indicated at the top of each column). The 99% confidence level is shown drawn through the data. When interocular latency differences were considered (Fig. 2b), a similar picture was observed in that no significant differences in the control and patient distributions or their respective means were noted.

As regards VEP amplitude, scattergrams of these data are presented in Fig. 3a. The large interindividual variability (which is characteristic of EP absolute amplitude measures in general) is seen in both control and patient groups. But even when this was allowed for there appeared to be a small shift to larger amplitudes in the distribution for (pretreatment) patients. This feature was confirmed when the means and standard deviations for the various groups were calculated. However, the increased mean in the pretreatment patient group was found to be not quite significant (0·05>p>0·01). Interestingly, what difference there was appeared to resolve in the post-treatment group. Analysis of interocular amplitude differences, of course, eliminates one source of interindividual variability and consequently results in much narrower distributions. These are illustrated in Fig. 3b. Once again there appeared to be some difference in the pretreatment group distribution in comparison with that for the control group. However, this was not significant when the respective means were compared statistically, though four individuals in this group were outside the 99% confidence limit. It is noteworthy that, after treatment, interocular differences in three of these four became insignificant.

Discussion

It is important in the study and application of evoked potentials that due consideration be given to the influence of sex and age on both diseased and control populations. VEPs are known to be affected by such factors,[8] and therefore to minimise their influence on the findings it is necessary to match control and pathological groups appropriately

From the results of this study it would seem that high levels of circulating thyroid hormone have little affect on conduction in the visual pathways, as no changes in VEP latency were observed. There may, however, be some influence which serves to increase VEP amplitude (a feature which agrees with previous observations utilising the flash VEP),[6] but the results of our trial are not statistically conclusive. In addition the broad distribution of this measure in both control and patient groups tends to militate against its use in routine clinical investigation. Thus, with the limited confidence which a trial of this size allows, we would conclude that hyperthyroidism has only a small affect on the VEP, both on presentation and throughout a course of treatment, notwithstanding the fact that no period of prolonged hypothyroidism has intervened.

The relevance of such findings in the management of thyroid eye disease must be that the observation of a delayed VEP is probably due to other factors (excluding other confounding neuro-ophthalmic disorders or artefacts due to optical or medial factors). This is certainly the case in patients who are hyperthyroid or euthyroid, and, while in hypothyroid patients some conduction delay may occur as a result of their thyroid status, it should be remembered that this does not occur in every case and, even when it does, only slowly after a prolonged alteration in thyroid hormone level.

The authors are indebted to Professor P Kendal-Taylor, Endocrine Unit, Royal Victoria Infirmary, for kindly granting access to patients investigated in this study, and to Mrs Karen Seed, senior medical physics technicians, who skilfully elicited a large proportion of the data

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Central compaction in the process of lens growth as indicated by lamellar cataract

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SUMMARY The lens growth through life is the net result of surface accretion partially offset by central compaction. Compaction has previously been shown to affect the cortex. The present study examines compaction in the nucleus by measuring the change in dimensions of congenital lamellar cataract with time and by comparing the different dimensions of dominantly inherited lamellar cataract in individuals of different ages in the same family. It is now shown that compaction affects the nucleus at a decreasing rate with increasing age and that the rate of compaction of lamellar cataracts is faster the greater diameter of the affected lamella. It is concluded that compaction of lens fibres towards the centre of the lens affects all regions of the cortex and nucleus in youth and that the compaction becomes largely or completely confined to the cortex in middle age and beyond. The shape of the lamellar cataract changes from a lenticular shape in youth to a rounded shape with increasing age. This accounts for the development of the peripheral divergence of the zones of discontinuity of the cortex, which allows the lens to remain emmetropic with increasing age in spite of changes in surface curvature.

The lens grows at a steady rate through life[1-6] by the process of surface accretion of new lens fibres offset by a central compaction of fibres towards the nucleus. An estimate of the compacting behaviour of the fibres in the cortex has previously been obtained by observing traumatic cataracts and glaucoma flecks.[7] These opacities occur initially in the immediately subcapsular region and sink into the lens with time. The study showed that the opacities sink in at approximately twice the rate at which the lens is growing, which implies that compaction is occurring at half the rate of the surface accretion. The study did not show to what depth in the lens the compaction proceeds. Is it a phenomenon limited to the cortex, or does compaction proceed all the way to the centre of the lens, or to some point in between? Does age affect this process, with compaction going all the way to the lens centre in youth and perhaps ceasing at a more superficial level in old age?

The present study examines congenital lamellar

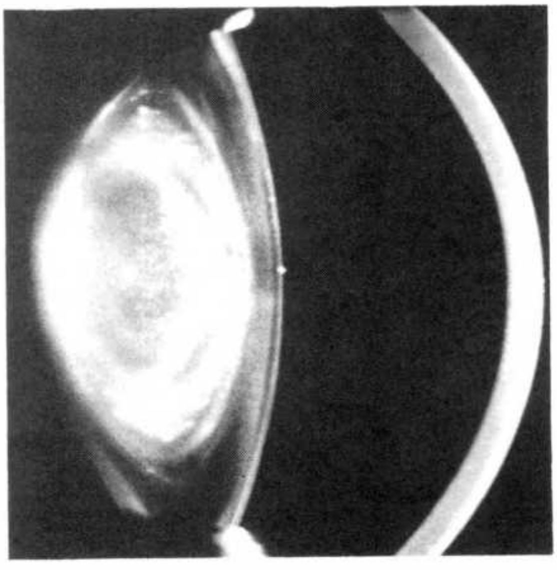

Fig. 1 *Subject aged 9 at first examination.*

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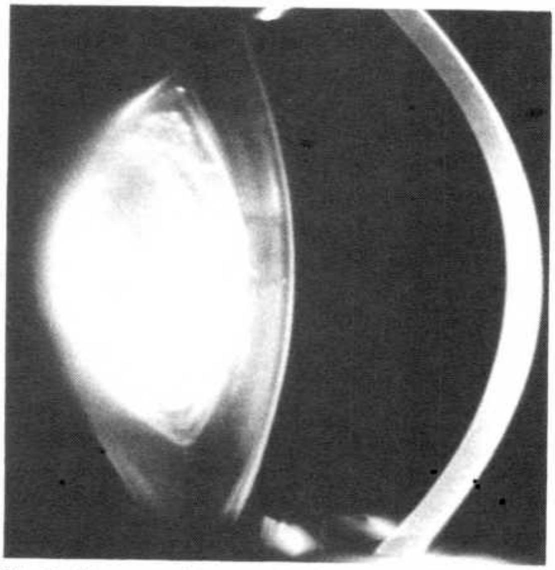

Fig. 2 *The same subject as in Fig. 1 at the age of 14.*

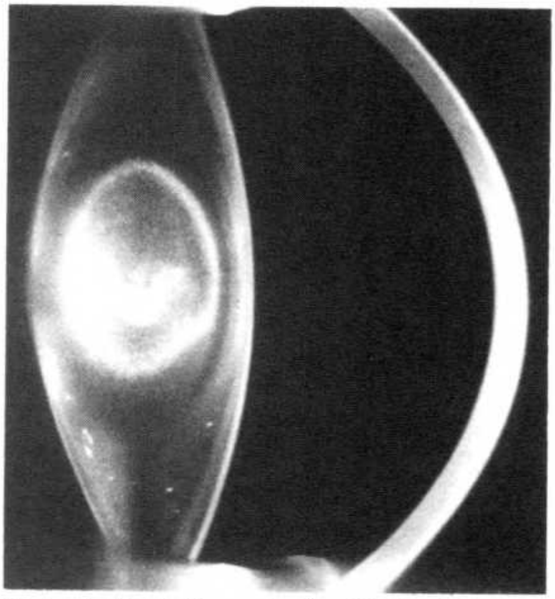

Fig. 4 *A subject in the same family as Fig. 3 aged 19.*

nuclear cataracts and their change with time in order to define how compaction affects the nucleus and to attempt to answer these questions.

Materials and methods

Subjects with congenital lamellar cataract (Figs. 1 and 2) were included when they had at least two slit-image photographic examinations at an interval of five or more years. A second group of subjects (Figs. 3 and 4) were included in which only single observations had been made in subjects who were members of a family with dominant congenital cataract. The inclusion of the familial group is justifiable if it can be presumed that the expression of the cataract was identical at birth in the separate individuals within each family. Some of the cataracts examined affected the complete nucleus and others only part of the central region of the nucleus. The extent of the nucleus affected in the familial group was the same in each individual in a particular family.

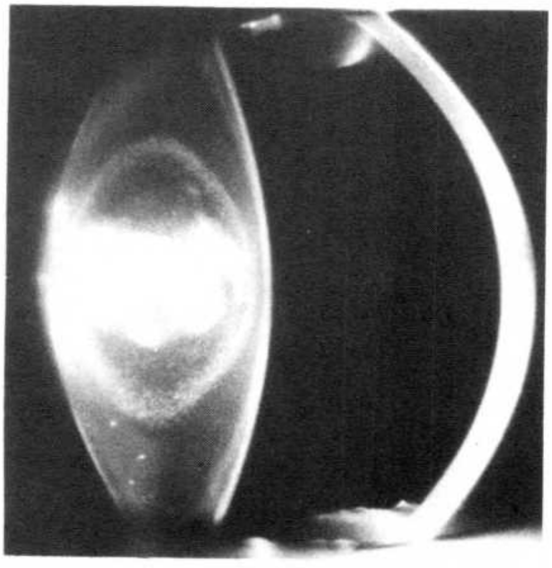

Fig. 3 *Familial congenital cataract in a subject aged 10.*

The subjects were examined by slit-image photography and then measurements made from negatives by a previously described technique.[8] The equatorial diameter and the sagittal width of the outermost affected lamella were measured. The measurements were corrected for camera magnifications but not for the magnification of the cornea or of the lens cortex. Two negatives were available for each eye in most cases, and the mean of the two measurements was taken. Left and right eyes of the same individual were found to behave in a very similar fashion and so the means of the left and right results were taken to illustrate the behaviour of the cataract in that individual (Figs. 5 and 6). (The averages were not used in the statistical analysis.)

Satisfactory negatives for measurement were obtained of five individuals on separate occasions and of one individual with a third examination. Four families with individuals of different ages were measured.

Table 1 *Younger lenses versus older lenses, paired t tests*

	Sagittal width			*Equatorial diameter*		
	Indiv	*Fam*	*Both*	*Indiv*	*Fam*	*Both*
Mean younger	2·81 mm	2·60 mm	2·70 mm	6·60 mm	5·04 mm	5·74 mm
Mean older	2·66 mm	1·98 mm	2·30 mm	6·18 mm	3·66 mm	4·80 mm
Mean age diff	8·6 yr	14·8 yr	11·9 yr	9·0 yr	19·0 yr	14·7 yr
Mean compaction per year	17 µm	42 µm	34 µm	47 µm	73 µm	64 µm
p Value	0·09	0·003	0·001	0·0005	0·001	0·001

Key to table: Indiv=individual patients, serial data, lens size when younger versus lens size when older. Fam=family groups, lens size of younger members versus lens size of older members p Value=significance level of paired *t* test comparing groups

Results

CHANGES IN THE DIMENSIONS OF LAMELLAR CATARACTS WITH AGE

The size differences between younger and older cataracts were examined statistically. Sagittal width and equatorial diameter were considered separately. The data from individual patients who had had two or more serial examinations were considered separately from those patients who were members of a family group. For serial examinations the initial cataract size was compared with subsequent cataract size in the same eye. Within the family groups, where only one examination per patient had been performed, the younger members of the family were compared with the older members. Finally the two groups were combined, with the individual patients and the family groups being considered together. The results of paired *t* tests between younger and older lenses are presented in Table 1. Apart from one group these results all showed a statistically significant reduction in cataract size at the 1% level. The exception was the group for serial measurement of the sagittal width of individual lenses over time. Although there was a trend towards a reduction in cataract size, this trend did not reach the 5% significance level. (This was the smallest group, and this fact may account for the statistically non-significant result.) These results confirm the impression that lamellar cataracts decrease in size over time.

RELATIONSHIP BETWEEN SAGITTAL WIDTH AND EQUATORIAL DIAMETER

A strong correlation existed between the sagittal width and the equatorial diameter of individual

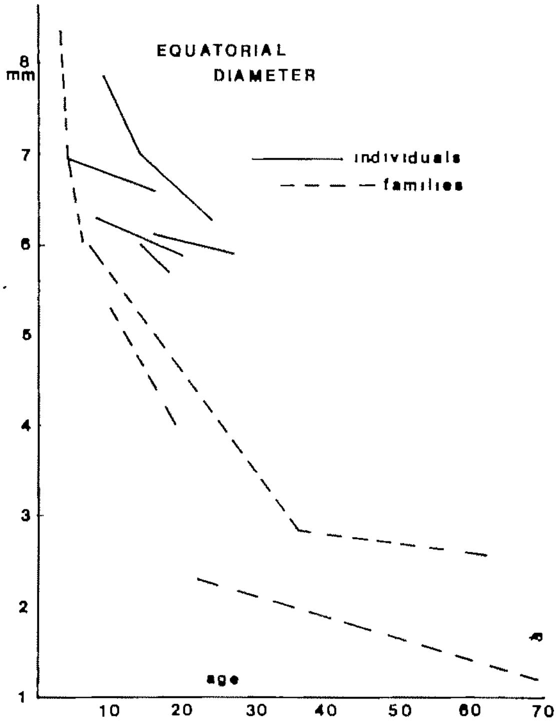

Fig. 5 *The change in equatorial diameter of lamellar cataracts with age.*

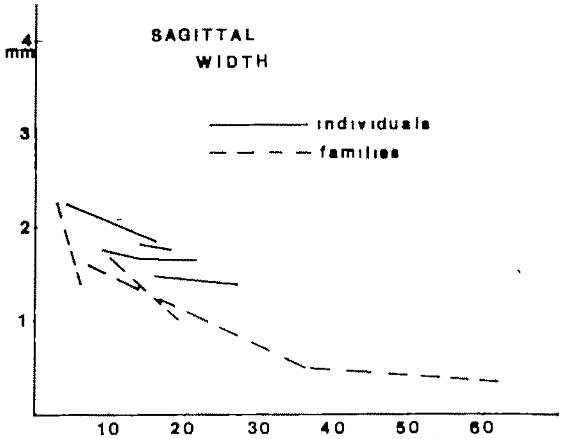

Fig. 6 *The change in sagittal width of lamellar cataracts with age.*

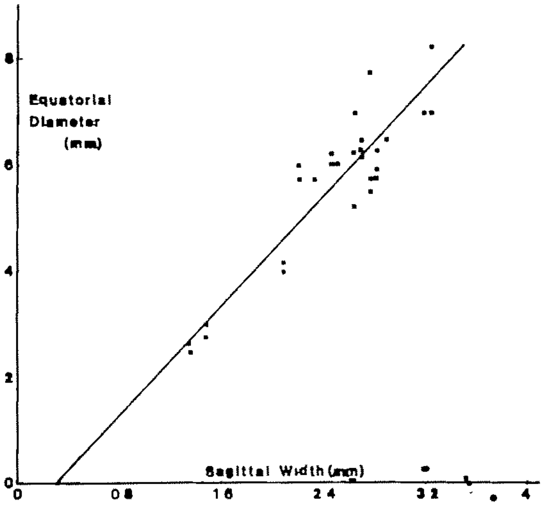

Fig. 7 *Correlation between sagittal widths and equatorial diameter of lamellar cataracts.*

lamellar cataracts. The linear correlation coefficient between these variables was 0·90, $p<0\cdot0001$). The linear regression line for the data was described by the function $Y=2\cdot56X-0\cdot75$ (SD for slope and Y intercept are 0·24 and 0·13 respectively. This regression line (Fig. 7) did not pass through the origin, and this relationship indicates that, the smaller the cataract is, the less oval and more round is its shape on sagittal section. This fact has important consequences for the refractive power of the growing lens as a whole, as discussed below.

RELATIONSHIP BETWEEN AGE OF PATIENT AND RATE OF CATARACT SHRINKAGE

Polynomial regression analysis of mean age against the rate of compaction of cataracts revealed a trend of decreasing rate of compaction of cataract with increasing age. A summary of the regression analysis for first order (linear) and second order (quadratic) polynomials is presented in Table 2. The linear regression lines all showed a typical trend of decreasing rate of cataract compaction with age. Examination of the relevant sections of the quadratic regression functions revealed a trend of rapid compaction in youth, which decreased with increasing age, and then settled down to a constant rate of compaction in about the third decade of life. There was one exception to this described trend, but in this set of data the correlation coefficient was not good ($r=0\cdot50$), and therefore the regression line may be unreliable.

Table 2 *Polynominal regression analysis of age versus rate of cataract shrinkage*

	Sagittal width			*Equatorial diameter*		
	Indiv	*Fam*	*Both*	*Indiv*	*Fam*	*Both*
Linear corr	0·73	0 61	0·46	0 25	0 65	0·47
Quad corr	0·80	0 74	0 69	0·50	0 82	0 71

Key to table Indiv=individual patients, serial data Fam=family groups Linear corr=linear correlation coefficient Quad corr=quadratic correlation coefficient

Table 3 *Polynominal regression analysis of initial cataract size versus rate of cataract shrinkage*

	Sagittal width			*Equatorial diameter*		
	Indiv	*Fam*	*Both*	*Indiv*	*Fam*	*Both*
Linear corr	0 88	0 63	0·46	0 58	0·75	0 48
Quad corr	0 89	0·79	0 61	0·78	0·97	0·72

Key to table Indiv=individual patients, serial data Fam=family groups Linear corr=linear correlation coefficient Quad corr=quadratic correlation coefficient

RELATIONSHIP BETWEEN INITIAL SIZE OF CATARACT AND RATE OF COMPACTION

Polynomial regression analysis of initial cataract size against the rate of compaction of the cataract revealed a trend of decreasing rate of compaction of cataract with decreasing initial cataract size. A summary of the regression analysis for first order (linear) and second order (quadratic) polynomials is presented in Table 3. The linear regression lines all showed a typical trend of decreasing rate of cataract compaction for smaller initial cataract size. Examination of the relevant sections of the quadratic regression functions revealed a trend of rapid compaction for larger cataracts, which tailed off towards a constant rate of compaction as the initial cataract size became smaller.

Discussion

CHANGE IN LENS COMPACTION WITH AGE

All individuals and families showed reduction in sagittal width and in equatorial diameter with increasing age. In some family groups the rate of reduction with age appears to be appreciably more rapid than in any of the individuals. This may be an artefact introduced by lack of identical genetic expression within each family at birth.

The rate of compaction of fibres is rapid in youth and decreases towards a constant slow compaction in about the third decade. The rate of compaction is also rapid for the initially large sized cataracts, and this

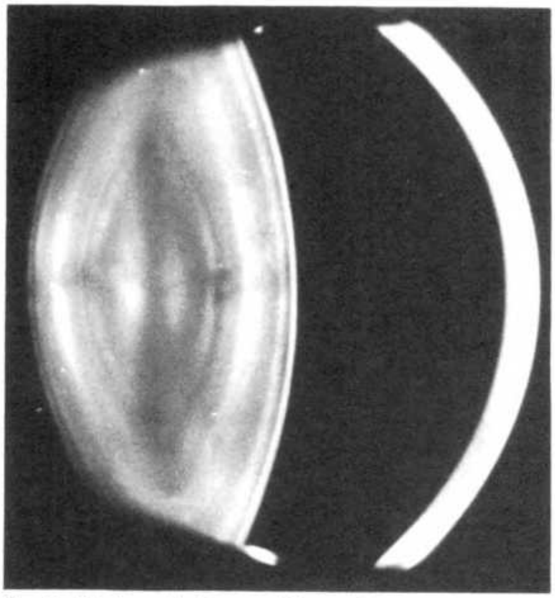

Fig. 8 *The lens of a 45-year-old normal subject showing peripheral divergence of the cortical zones of discontinuity.*

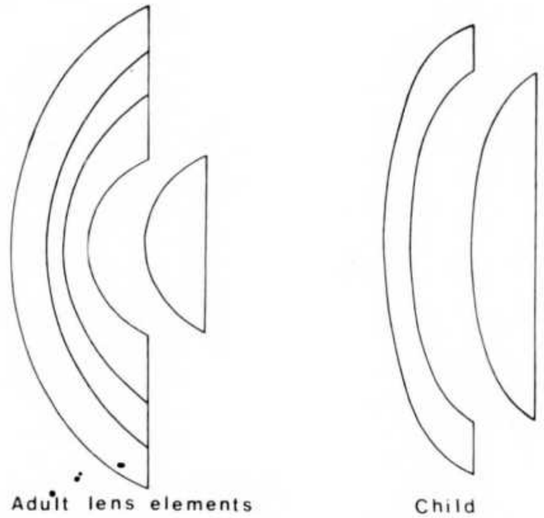

Fig. 9

slows as cataracts get smaller. Because the lamellar cataracts examined become smaller with increasing patient age (saggital width, linear correlation coefficient=0·83, p<0·0001; and equatorial diameter, linear correlation coefficient=0·81, p<0·0001), we can conclude that large lamellar cataracts are seen in young individuals, and that these rapidly compact down in youth to smaller slowly compacting cataracts in the older patients. From the previous study of initially subcapsular cataracts[7] it was shown that cortical compaction was occurring in the lenses at all ages studied and that the rate of compaction was independent of the age of the individual. It was shown that the rate of compaction was faster the nearer the opacity was to the lens surface, and it was concluded that compaction was largely a cortical phenomenon. (We regard the nucleus as being the part of the adult lens which corresponds to that which comprised the whole of the lens at the time of the birth of the individual.) It can now be stated that compaction of lens fibres towards the centre of the lens affects all regions of the cortex and nucleus in youth and that the compaction becomes largely or completely confined to the cortex in middle age and beyond.

These findings are compatible with what is known of the change in physical characteristics of the nucleus and cortex with age. Fisher[9] has shown that the elasticities of the lens cortex and nucleus change with age from a more deformable nucleus than cortex in youth, to a less deformable nucleus with age. It seems probable that the change in Young's modules of elasticity with age that Fisher measured affects the ability of the lens fibres to compact and can account for the present observations that rapid fibre compaction affects the nucleus in youth and that this slows with age. Nordmann *et al.*[10] showed that the dimensions of the nucleus increase with age, when the border of the nucleus is defined by the identification of the region of increased resistance to physical penetration of the lens. It is to be noted that the measurement of sagittal width of the nucleus by biomicroscopy[4 11-13] and by slit-image photography[6 14 15] shows it to increase very little with age and that lens growth is mainly cortical. Nordmann and colleagues, findings[10] of the apparent growth of the physically more resistant 'nucleus' with age are compatible with the present suggestion that the depth to which compaction proceeds becomes more superficial as the lens ages.

CLINICAL SIGNIFICANCE

The reduction in equatorial diameter with age of congenital lamellar cataracts should result in improving vision in the affected children. This was suggested[16] from some early observations on congenital cataract. The reduction in diameter of lamellar cataracts with age is now confirmed, so it may be concluded that, in those cases in which mydriasis gives adequate vision in infancy, cataract extraction can be avoided. However, three families (not included in the present study) have been observed in which the cataract increases in size by the addition of new opaque lammellae superficial to the congenitally formed opaque lamella. Thus continuing observation is important.

SHAPE OF NUCLEUS AND MAINTENANCE OF EMMETROPIA

The tendency of the eye to maintain emmetropia, or in fact slightly increasing hypermetropia[17,18] through life, in spite of continuing growth of the lens has remained a fascinating enigma This was conveniently explained by earlier workers,[19] since Donders[20] described an increasing radius of curvature of the lens surfaces with age. Recent work demonstrates that the radius of curvature of the lens surfaces in fact become shorter with age.[21,22] This increased curvature of the lens surfaces would be expected to cause myopia, which does not normally occur, and therefore it must be offset by changes in the physical characteristics within the lens.

Our new data (regression line in Fig. 7) show that the outer lamellae of the lens are more lenticular in shape than are the inner lamellae. We are thus witnessing two processes of shape change in the lens. Firstly, the whole lens is becoming rounder (less lenticular) with age, and secondly the lamellar shells are becoming rounder with topographical passage deeper into the lens. It is this second process which gives rise to the peripheral divergence of the zones of discontinuity of the cortex, which is well seen in the 5th decade (Fig. 8). Duke-Elder,[23] who was not then aware of these changes in lens shape with age, proposed that the lens could be treated as three separate optical components: a biconvex nuclear element and two meniscus cortical elements (Fig. 9). The present study suggests that in terms of curvature the nucleus should become more positive with age. The cortex should become more negative with age, since the change in curvature is greater at the deep surface than it is at the outer surface (Fig. 9).

Duke-Elder considered that the lens would have maximal refracting power when the greatest difference in refractive index existed between the higher refractive index nucleus and the lower refractive index cortex and that such a lens would have greater refracting power than if it were a homogeneous structure of the higher of the two refractive indices. If the refractive indices of the nucleus and cortex remained unchanged with age, it might be expected that the increased curvature of the nucleus would more than offset the cortical negative change and induce myopia. It is thus necessary for the refractive index of the cortex to rise with age,[24] but it cannot be assumed that the cortex is homogeneous in terms of refractive index, and it probably varies in the different zones of discontinuity. This seems highly probable, since the theory of light scatter in the normal lens relates scatter to refractive index.[25]

The individual cortical zones of discontinuity have already been considered to be separate iso-indicial surfaces.[26] Since these zones displaying peripheral divergence develop with age, they may be considered as individual negative lens elements when the refractive index of a particular zone exceeds that of the adjacent zones (Fig. 9).

In conclusion, it appears that emmetropia in aging is maintained by a balance between increasing refractive power of the lens due to increasing curvature of the lens surface and of the surface of the nucleus balanced by reducing refractive power due to an increasing refractive index in the cortex as a whole, and in individual peripherally divergent brightly scattering zones of discontinuity in the cortex in particular.

Lens growth throughout life by the continued mitosis of the lens epithelial cells to form new lens fibres may be inevitable, because the lens is an epithelial structure, but is more likely to be purposeful to ensure that the lens is always surrounded by a layer of young metabolically active fibres. The lens then has the task of accommodating these new fibres without excessive increase in size and without inducing myopia. This is achieved most beautifully by central compaction of the lens fibres asymmetrically, leading to the nucleus becoming more spherical and to peripheral divergence of the cortical zones of discontinuity.

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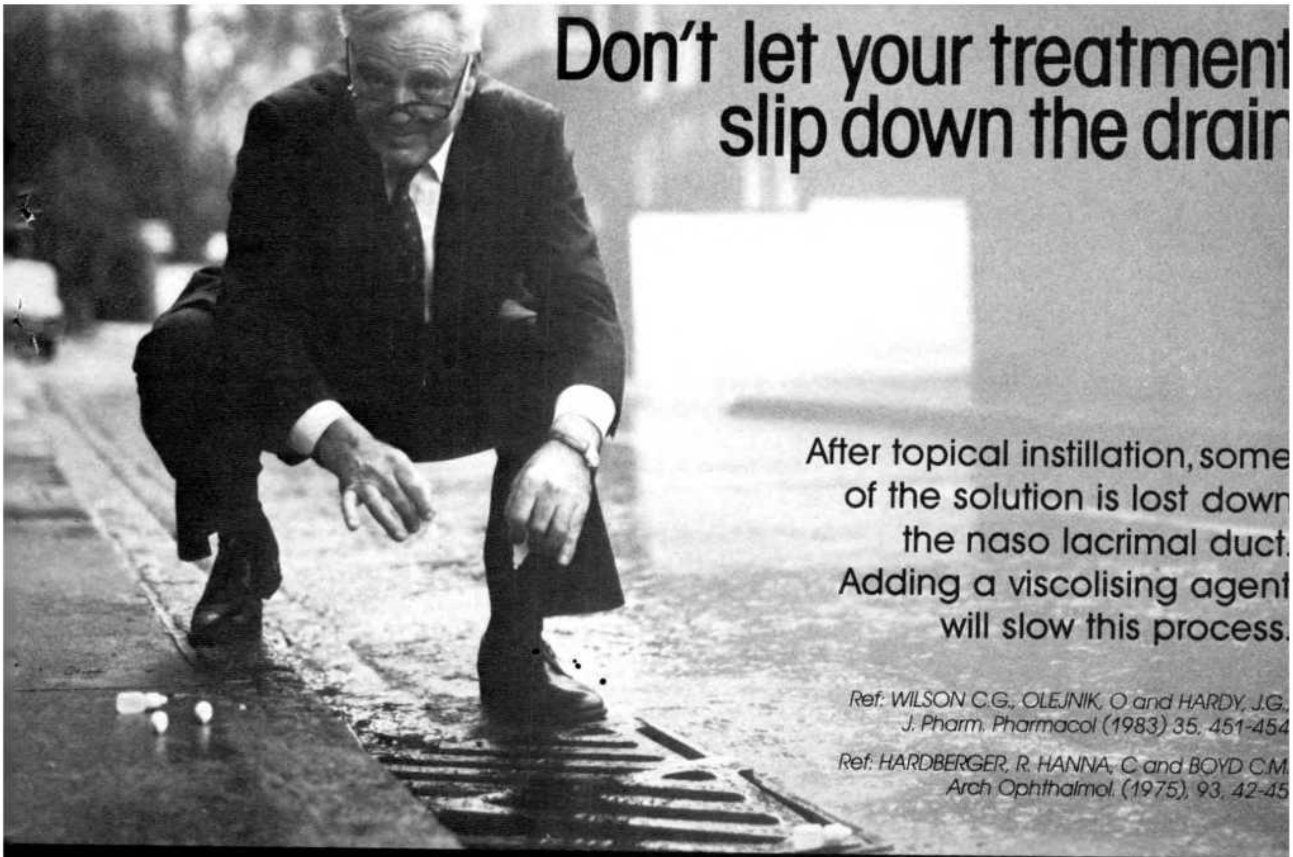

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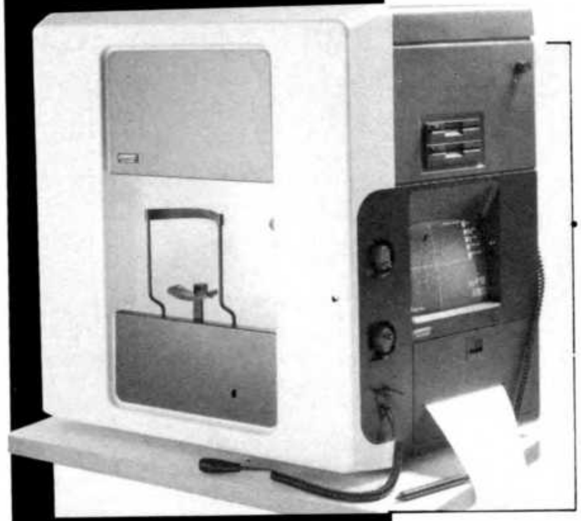

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A morphometric study of endothelial cells of human corneas stored in MK media and warmed at 37°C

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SUMMARY No study has yet been done to investigate the changes in endothelial cell size, perimeter, and density that may result from the warming of corneas in MK (McCarey-Kaufman) medium for specular microscopy. In the present investigation eye bank eyes were stored in MK medium at 4°C and rewarmed daily for six days at 37°C before specular photography of the endothelium was performed. These photographs were compared with wet mount preparations stained with trypan blue and alizarin red made from the same corneas and those stored without rewarming for six days. In addition all corneas were qualitatively analysed with the scanning electron microscope (SEM). The data from serial specular photography were insufficient to allow significant conclusions to be drawn about day to day changes in cell morphology. However, analysis of wet mount preparations revealed that cell density and perimeter varied significantly between those corneas rewarmed daily and those held in cold storage for six days. SEM studies showed an intact cell monolayer with cell loss along the folds of corneal endothelium. We therefore concluded that repeated rewarming at 37°C of corneas stored in MK medium at 4° has a deleterious effect on cell morphology and that folds induced by swelling of corneal tissue result in endothelial cell damage with some loss.

The morphological study of the corneal endothelial monolayer has been greatly facilitated by the advent of specular microscopy.[1] This has allowed for viewing of the living endothelium both in vivo[2] and in vitro.[3] Initial studies looked at cells in terms of density,[4] that is, cells per unit area. These density calculations did not always provide an accurate prediction of cell function.[5] Consequently investigators have been looking at other parameters to quantitate cell size variability (polymegethism) and cell shape variability (pleomorphism).[6,7]

We wanted to answer a question that often worries eye bank personnel: Do the characteristics of endothelial cells of corneas stored in the MK (McCarey-Kaufman) medium at 4°C change when corneas are briefly warmed at 37°C for specular microscopic examination?

For the purpose of studying the variables of corneal endothelial cell density, mean cell area, and cell perimeter, chronological specular photographs were compared with photographs taken of an endothelial wet mount preparation from the same cornea at the end of the storage period.

Materials and methods

Five pairs of human donor corneas were put in MK medium within 12 hours post mortem. One of each corneal pair was placed in MK medium in a corneal viewing chamber (Product Research Organization (PRO) Inc., Tustin, California). This cornea (experimental cornea) was stored at 4°C, removed daily, and warmed at 37°C for one hour for six days. The endothelium was then photographed with the specular microscope (PROEB-I). Afterwards the cornea in the storage chamber was returned to cold storage. The other cornea of the pair acted as a control and was put in a vial of MK medium at 4°C continuously for six days. After six days of storage each cornea was removed and bisected. One half of the cornea was processed for scanning electron microscopy by the method described previously.[8] The other half was stained with trypan blue and

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alizarin red[9,10] with the endothelium being photographed as a wet mount preparation.

To count the cell density (cells per square mm), individual cell area, and cell perimeter all the photographs of the wet mount photographs and calibration grid (0·01 mm) were magnified to 428 times. The cell boundaries in each photograph were enhanced manually with a felt tip marker. A quantitative morphometric analysis of the cells was done with an image analyser (Omnicon 3000 Bausch and Lomb, attached to a computer: Nova IV Data General), located at the Department of Mechanical Engineering, University of Toronto.

Results

SPECULAR MICROSCOPY

Good quality photographs were obtained when the cornea and its MK medium was warmed at 37°C for 1 hour. Since the quality of specular photomicrographs varied daily at different sites of the same cornea, it was not possible to have data from all corneas suitable for statistical analysis. Table 1 shows the number of photographs available for each cornea on each day of observation. It was possible, however, by comparing the photographs on a daily basis to detect changes in endothelial cell shape and size. Figs. 1 and 2 show a qualitative comparison of specular images of similar areas of an experimental donor cornea photographed after one and six days of storage. There is a more compact cellular structure in the corneal endothelium stored for 1 day (Fig. 1) than in the same corneal endothelium photographed after six days of storage (Fig. 2).

Table 1 *Number of specular photographs available on each day of observation*

Eye Bank number	*Day*						
	0	*1*	*2*	*3*	*4*	*5*	*6*
19053	3	1	–	–	1	2	2
19059	2	–	2	1	2	3	–
19075	–	2	2	–	–	–	–
19095	1	–	1	–	–	1	–
19103	2	6	–	–	2	–	–

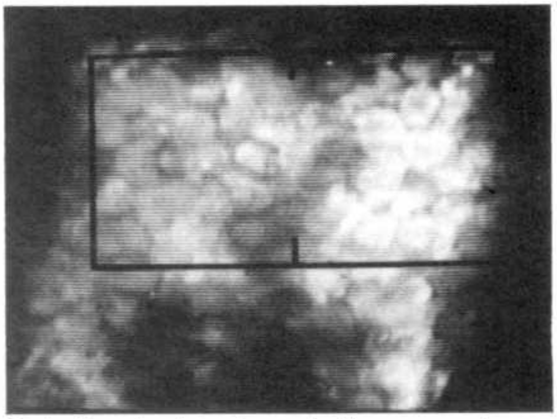

Fig. 1 *Specular photomicrograph of human corneal endothelium after one day of storage in MK medium at 4°C. Cornea was warmed at 37°C for one hour. Note photograph shows some guttae.*

LIGHT MICROSCOPY OF WET MOUNT PREPARATION

The comparative data of the experimental and the control corneas in terms of changes in cell density, mean cell area, and perimeter are shown in Table 2. By means of the unpaired *t* test it was found that mean cell area and perimeter in the control corneas was significantly smaller in three out of five pairs than in the corresponding experimental corneas (Table 2). When the difference was analysed with the paired *t*

Table 2 *Endothelial morphological analysis from wet mount photographs of corneas stored in MK medium at 4°C (controls) compared with corneas in MK medium that were rewarmed daily to 37°C for one hour (experimental)*

Donor number	*Eye bank no.*	*Sample*	*No. of cells*	*Mean cell area ± SD (μm²)*	*Coefficient of variation of cell area*	*Cell density (mm²)*	*Cell perimeter ± SD (μm)*	*Coefficient of variation of perimeter*
1	19054	Cont.	(136)	267±122	0·45	3738	64·2±14	0·21
	19053	Expt.	(45)	369±118**	0·32	2710	74·9±12*	0·16
2	19060	Cont.	(198)	201±86	0·43	4955	55·5±11	0·20
	19059	Expt.	(172)	222±108*	0·45	4489	58·7±13*	0·23
3	19076	Cont.	(192)	205±81	0·39	4859	56·4±11	0·20
	19075	Expt.	(131)	222±119	0·53	4504	59 ±16	0·27
4	19096	Cont.	(190)	212±105	0·49	4714	56·8±13	0·22
	19095	Expt.	(15)	209±100	0·47	4780	56·6±13	0·23
5	19104	Cont.	(221)	180±81	0·44	5527	52 ±11	0·21
	19103	Expt.	(186)	212±114**	0·53	4714	56·3±16*	0·28

Significant values: *$p<0·05$; **$p<0·01$. Cont. = control. Expt. = experimental.

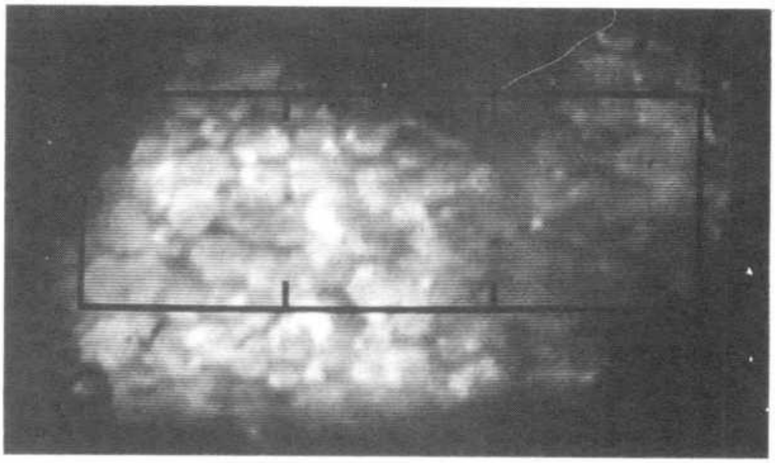

Fig. 2 *Specular photomicrograph of similar area of corneal endothelium as in Fig. 1 after six days of storage. The cornea was rewarmed daily at 37°C for one hour. Note the presence of larger cells and greater guttae than in Fig. 1 (control).*

test, it was found that mean cell area in the total sample did not vary significantly ($p>0\cdot05$), whereas the cell density and perimeter varied significantly ($p<0\cdot05$ and ($p<0\cdot02$ respectively) (Table 3).

SCANNING ELECTRON MICROSCOPY

It was observed that in both experimental and control corneas a monolayer of cells was present, though it tended to be damaged or absent in areas overlying folds (Fig. 3). In these areas cells had rounded and had lost continuity with their neighbours. This was also true of the cells along the folds in wet mount preparations (Fig. 4). In the wet mount preparations dead cells, indicated by darkly stained nuclei, were observed to lie in aggregates along a fold of corneal endothelium (Fig. 4). In some areas exposed Descemet's membrane was observed staining red with the alizarin red.

Discussion

Specular microscopy of eye bank corneas is a technique being utilised increasingly. Better storage chambers and microscopes have facilitated this increase. Difficulties with the systems still remain. It is not always possible to obtain good quality photomicrographs even immediately on the eyes' arrival in the eye bank. It was found in our laboratory that image quality was poorer with storage greater than 48 hours. This is in agreement with the observations of

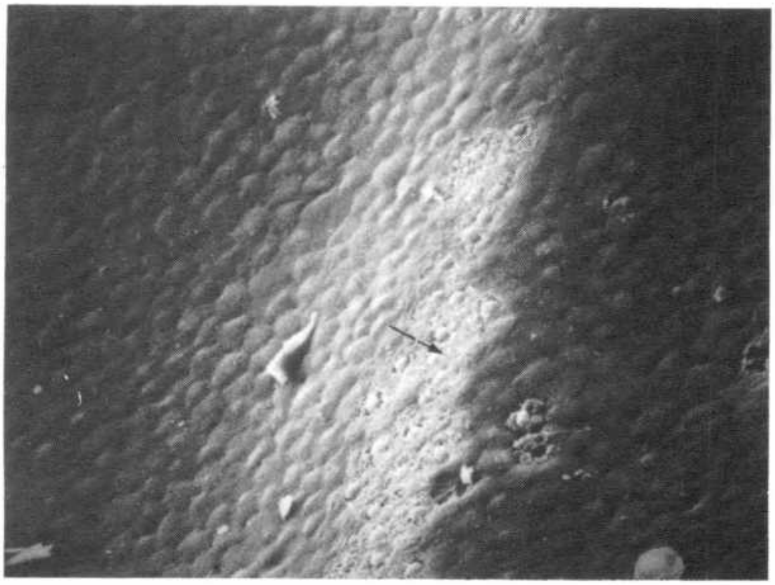

Fig. 3 *Scanning electron micrograph of human corneal endothelium stored in MK medium at 4°C for six days (control). Arrows show dying cells along the fold.*

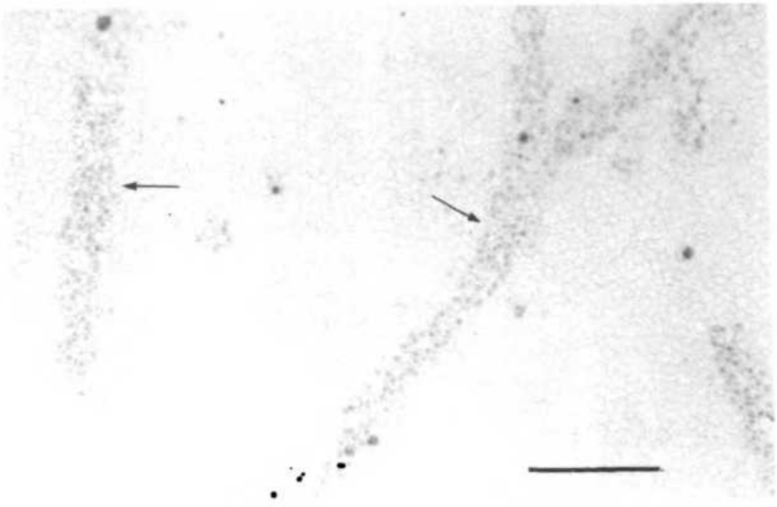

Fig. 4 *Photograph of human corneal endothelium stained with trypan blue and alizarin red after storage in MK medium at 4°C for six days (control). Arrows show the non-viable cells along the fold. Bar=200* µm.

Nesburn *et al.*,[11] who reported similar problems in endothelial examinations by specular microscopy. However, it was observed that an increase of the incubation period at 37°C facilitated observation. In addition, while specular photography may have been quite poor, when corneas were later stained with alizarin red and trypan blue an intact endothelial monolayer was found to be present. Another problem with the specular microscope is that on any given day of observation it may be possible to photograph only 30–40 cells despite a thorough search of the entire cornea. This is due to the optical system of the specular microscope and concavity of the cornea. A low power objective lens may help in scanning the entire endothelial surface and alleviate this difficulty. This makes it difficult to know whether these few cells truly represent the entire monolayer. Moreover it is impossible to identify conclusively the same exact area in sequential observations.

Because of these problems it was difficult to obtain sufficient data to analyse changes occurring on a day-to-day basis and to compare specular microscopy values with the wet mount preparations values. However, there is an indication from the specular photography in this study that cell area and perimeter of corneal endothelial cells increase with storage time (Figs. 1, 2).

Table 3 *Pooled data from analysis of wet mount photographs from corneas stored in MK medium at 4°C (control) and those rewarmed daily to 37°C for one hour daily (experimental)*

	Mean cell area±SD (μm^2)	*Cell density±SD* (mm^2)	*Cell perimeter±SD* (μm)
Cont. n=5	213±32	4759±289	56·98±4·4
Expt. n=5	246±68	4239±386	61·1 ±7·8
	t=1·8	t=2·7	t=4·12
4 DF*	p<0·01	p<0·05	p<0·02

*DF=degrees of freedom.

From the wet mount preparations it was also seen that, when all pairs of corneas were compared, there was no significant increase in mean cell area as a result of rewarming and storage. Cell density and perimeter did, however, vary at levels of significance of 5% and 2% respectively. Intraindividual variation amongst paired corneas varied significantly for mean cell area and perimeter in three out of five corneas.

These results (Tables 2 and 3) suggest that rewarming at 37°C of the experimental corneas (kept in MK medium at 4°C) had a deleterious effect on endothelial cell morphology. However, a larger sample is necessary to assess further whether mean cell area is affected, since in our study the mean cell area was not significantly different between the experimental and control groups when the data were pooled.

Scanning electron microscopy served to illustrate that, even when specular microscopy may not image the endothelium of eye bank eyes in MK medium, viable cells are present. It also showed that cell death occurred along folds of corneal endothelium. The folds seen in SEM correlated well with folds seen on the wet mount preparations (Figs. 3 and 4). The folds may be created by imbibition of water by the stored cornea stroma. This suggests that methods of storage which result in greater swelling of stored tissue may induce more damage to endothelial cells, and, conversely, those methods which reduce tissue swelling may be beneficial in reducing endothelial disruption during storage. Moreover surgical techniques that reduce bending and folding of corneal tissue may result in less endothelial cell loss and a more favourable surgical outcome.[12]

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Lamellar macular hole associated with idiopathic juxtafoveolar telangiectasia

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SUMMARY A case of juxtafoveolar telangiectasia complicated by lamellar, retinal hole is reported and the pathogenesis discussed. This association is not commonly recognised.

Idiopathic juxtafoveolar telangiectasia is a relatively rare condition predominantly affecting adult males.[1] Visual disturbance in retinal telangiectasia is usually due to vascular leakage, with intraretinal oedema and exudate accummulation and later cystic degeneration.[1] Subretinal neovascularisation with a disciform response may also contribute to a poor visual outcome. In this report we describe a case of unilateral idiopathic juxtafoveolar telangiectasia with central visual loss due to a lamellar macular hole.

Case report

A 37-year-old Caucasian was found in the course of a routine eye test to have a central visual acuity of 6/18 in the left eye. The visual acuity in the right eye was 6/5. Both anterior segments were normal, as was the right fundus. There was an incomplete ring of circinate exudate round the left fovea, with a lamellar hole at the fovea (Fig. 1).

The patient was in good general health and in particular was not diabetic or hypertensive. An oral glucose tolerance test was normal. There was no history of ocular trauma, inflammation, or vascular disease.

Fluorescein angiography showed a cluster of telangiectatic vessels at the centre of the exudate, and a smaller area of telangiectatic vessels inferotemporal to the lamellar hole (Fig. 2). There were widespread but discontinuous areas of telangiectatic vessels in all peripheral quadrants. The larger area of abnormal vessels was treated with argon laser, which brought about a significant diminution of hyperfluorescence on angiography but had no effect on the exudate or the visual acuity over the five-month follow-up period.

Discussion

The term idiopathic retinal telangiectasia was proposed by Reese[2] to define a spectrum of congenital vascular anomalies which includes Coats' disease, Leber's miliary aneurysms, and juxtafoveolar telangiectasia. These are to be distinguished from secondary forms of telangiectasia associated with branch vein occlusion, diabetes mellitus, sickle cell retinopathy, carotid artery occlusion, and radiation retinopathy.

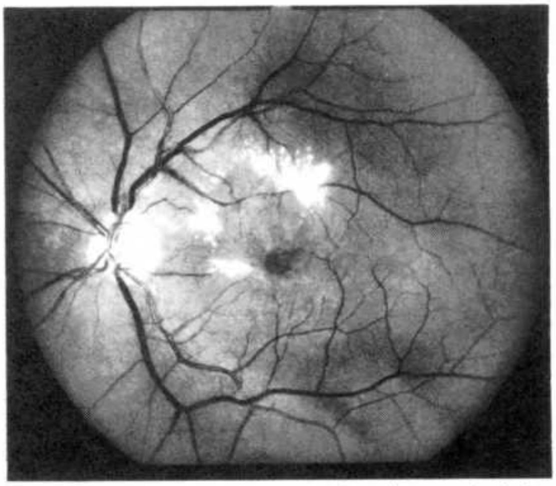

Fig. 1 *Fundus photograph showing lamellar macular hole with circinate exudate.*

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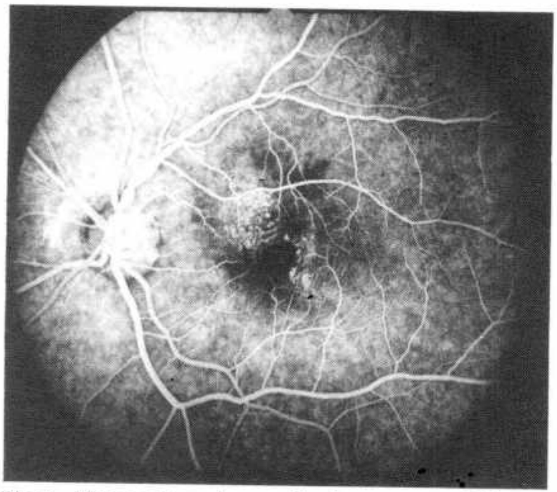

Fig. 2 *Fluorescein angiogram showing two areas of vascular telangiectasis, one superonasal and the other inferotemporal to the fovea.*

Gass and Oyakawa[3] reported the findings in a series of 27 cases of idiopathic juxtafoveolar telangiectasia and classified the condition into four groups. The first group, into which our patient loosely fits, comprised eight males and was characterised by uniocular involvement, with telangiectasia confined to the temporal half of the macula, symmetrically distributed above and below the horizontal raphe. Visual loss was a consequence of macular oedema. In the other three groups both eyes were affected, and the cause of visual loss was subretinal neovascularisation as well as macular oedema. In the series there were no cases with macular hole in group 1, but in the other groups there was one patient who developed a macular hole and one case of retinal thinning. In a series of 46 cases reported recently by Casswell and colleagues[4] no macular holes were seen.

We are aware of only two other case reports of macular hole associated with retinal telangiectasia. One of these is in a case of Coats' disease[5] and the other in a histopathological review of macular holes.[6]

Macular holes most commonly occur as a sequel to macular oedema.[6,7] We are surprised that they have not been more frequently found in association with telangiectatic lesions, since it appears beyond dispute that leakage from the abnormal vessels causes intraretinal oedema. This might be expected to induce local destruction of the retina with the formation of cysts and ultimately holes.

We could speculate that in unilateral idiopathic retinal telangiectasia the lesion is largely limited to the locally involved vessels, whereas in other forms of macular oedema the retina itself is affected by a more widespread circulatory or haemodynamic abnormality giving rise to the oedema. In the latter case there may be less resistance from compromised tissues to intraretinal fluid destroying adjacent structures, forming cysts and ultimately holes. In unilateral cases with no widespread defect the more healthy adjacent areas of retina may maintain their architecture in the presence of oedema fluid. Both the case showing the macular hole and that showing retinal thinning in the series were in the bilateral groups.

Only in bilateral cases in the series of Gass and Oyakawa[3] was subretinal neovascularisation or a disciform response seen. This may be interpreted as an indication of more generalised retinal disturbance, probably of ischaemic nature, rather than the localised vascular malformation of unilateral cases. Our hypothesis fits with the findings recently reported by Casswell *et al.*,[4] who suggest that unilateral disease is indicative of a vascular abnormality, whereas bilateral disease may indicate a pigment epithelial defect.

Recently it has been reported that abnormalities of glucose tolerance may be found in cases previously diagnosed as idiopathic juxtafoveal telangiectasia.[8] Among 28 patients five out of eight bilateral cases had abnormal glucose tolerance, while only six out of 17 unilateral cases showed any abnormality. These results give some support to the hypothesis that bilateral disease occurs in relation to a widespread metabolic disturbance in the retina, whereas unilateral cases represent a local and truly vascular defect.

We would then expect macular holes to occur more frequently in association with secondary retinal telangiectasis. This hypothesis will be investigated.

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Acquired Brown's syndrome in a patient with combined lichen sclerosus et atrophicus and morphoea

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SUMMARY A 49-year-old woman with generalised lichen sclerosus et atrophicus and morphoea developed bilateral Brown's syndrome. Some of the skin lesions were in the vicinity of the trochlea. A characteristic feature of morphoea is subcutaneous fibrosis, so we postulate that the cause of the Brown's syndrome was mechanical tethering of the superior oblique tendon by deep subdermal fibrosis. Histopathological diagnosis was made from biopsies of similar lesions on the patient's face.

In 1950 H W Brown[1] first published his series of seven cases with the following clinical features: slight downdrift of the affected eye on adduction; limitation of elevation on adduction; widening of the palpebral fissure on adduction; no overaction of the ipsilateral superior oblique; V exo pattern; positive traction test.

He suggested that this syndrome was due to congenital paralysis of the inferior oblique muscle resulting in a short anterior superior oblique tendon sheath. In a further publication[2] he divided his cases of superior oblique tendon sheath syndrome into two types—true and simulated cases. The true cases were those with a congenitally short anterior sheath of the superior oblique tendon. These patients had a positive traction test. The simulated cases were all others, either congenital or acquired The congenital simulated cases were postulated to have a thick posterior tendon or firm attachment of the posterior sheath to the tendon. The acquired cases were of inflammatory origin.

In 1975 Parks and M Brown[3] reviewed the theories of true Brown's syndrome and were unable to demonstrate H W Brown's findings of a short anterior sheath except in two of the 24 patients in whom they had surgically explored the orbit. They suggested that the usual cause of Brown's syndrome was a restrictive connective tissue band situated posteriorly and inferiorly to the globe. In 1977 Parks[4] suggested that Brown's syndrome was due to a taut tendon for which tenectomy was effective treatment and remarked that the superior oblique tendon did not have a sheath, but that the anterior half of the tendon actually penetrated Tenon's capsule, to which it was attached by an elastic connective tissue sleeve.

Whereas true Brown's syndrome, which often resolves spontaneously or can be treated surgically, has a limited number of causes, acquired Brown's syndrome is a diverse group that is often difficult to treat, particularly if the syndrome is caused by trauma. Acquired Brown's syndrome occurs rarely and usually in an older age group than true Brown's syndrome of childhood.[1 2] Non-traumatic inflammatory causes of acquired Brown's syndrome have been reported to include frontal sinusitis,[5] rheumatoid arthritis,[6-8] and juvenile chronic arthritis.[9 10] No obvious cause may be found in some cases.[11] Traumatic causes are either surgical (following frontal sinus surgery[12] or a superior oblique tuck[13]) or more commonly non-surgical,[14] when a sharp instrument enters the upper nasal quadrant of the orbit. Occasional cases have been reported as having other more unusual causes such as a secondary deposit in the orbit from a primary carcinoma of the prostate.[15]

The present case report describes an additional cause of acquired Brown's syndrome—combined lichen sclerosus et atrophicus and morphoea. An understanding of the histological changes in this skin condition indicates one mechanism for the diplopia in some cases of acquired Brown's syndrome and thereby provides a rational basis for the management of the ophthalmic problems in such cases.

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Case history

A 49-year-old woman with a clinical and histological diagnosis of lichen sclerosis et atrophicus and morphoea was referred from the dermatology clinic in August 1984 because of increasing diplopia. She had first noticed double vision 12 months previously. This had become increasingly noticeable, particularly on looking up and to the left.

One month after the onset of diplopia the patient developed discrete firm white plaques round the right eye extending on to the forehead. Similar plaques became apparent round the left eye. She noticed a bullous lesion on her hip and a large skin lesion on her neck, for which she sought the advice of a dermatologist. A biopsy was taken from the bullous lesion on her right hip, and histological examination indicated a diagnosis of morphoea.

Within a few months she also developed patches of scaly depigmentation on her right cheek and on the front of her neck, with a larger area affecting her forehead in an 'en coup de sabre' distribution (Figs. 1A, B). This lesion extended to the midline of the forehead, up into the scalp, where there was associated frontal alopoecia, and down over the superonasal quadrant of the orbit to the lid margin nasally with associated loss of cilia and supracilia. There was a thickened area of skin over the region of the right trochlea and the right interpalpebral fissure was narrowed by 1·5 mm in comparison with that on the left. The discrete lesions over the left brow and superonasal orbit became more noticeable with time. Later two further biopsies from her cheek and forehead showed combined lichen sclerosus et atrophicus and morphoea.

She had a corrected visual acuity of 6/4 in each eye and had a compensatory head posture consisting of chin elevation and a small head turn to the left, with which she avoided diplopia in the primary position. She had an exotropia in elevation and an exophoria in the primary position when wearing glasses. There was slight underaction of her right eye on laevo-elevation and minimal underaction of her left eye on dextro-elevation (Fig. 2). Her diplopia was most marked on laevo-elevation. No click was heard or felt over either trochlea. The Hess chart (Fig. 3A) was consistent with a bilateral Brown's syndrome, more marked on the right than the left. In the right eye a

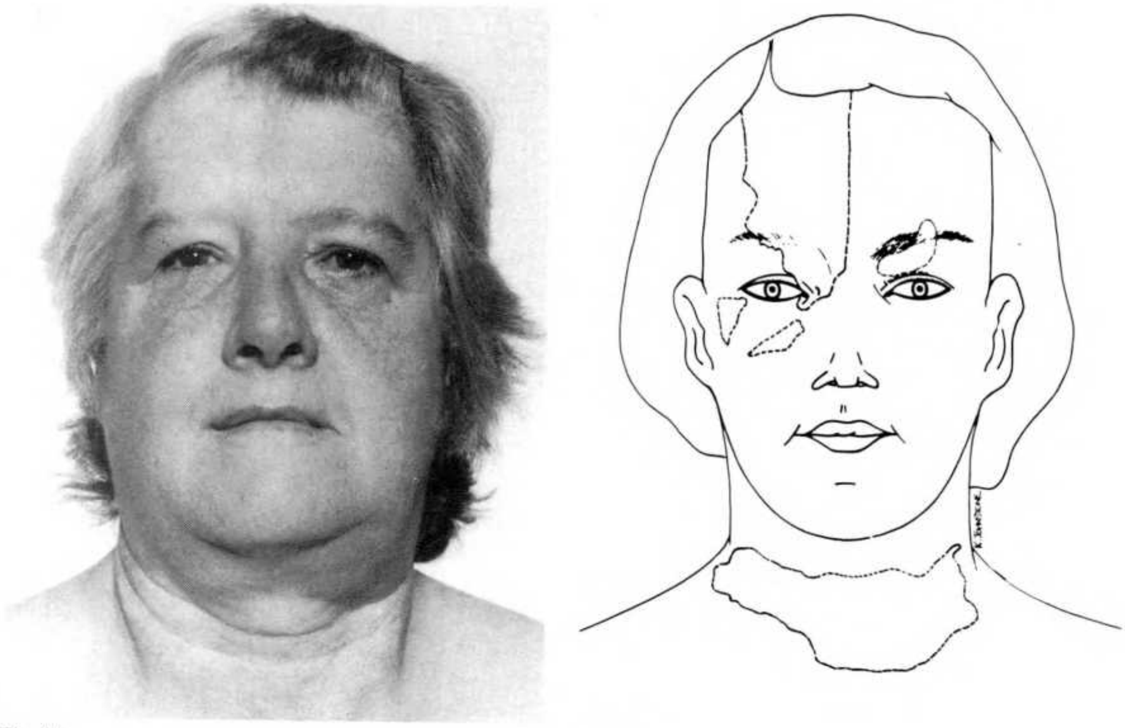

Fig. 1A

Fig. 1B

Figs. 1A, B *Distribution of plaques and en coup de sabre lesion of lichen sclerosis et atrophicus. These lie over the region of the trochleae on both sides.*

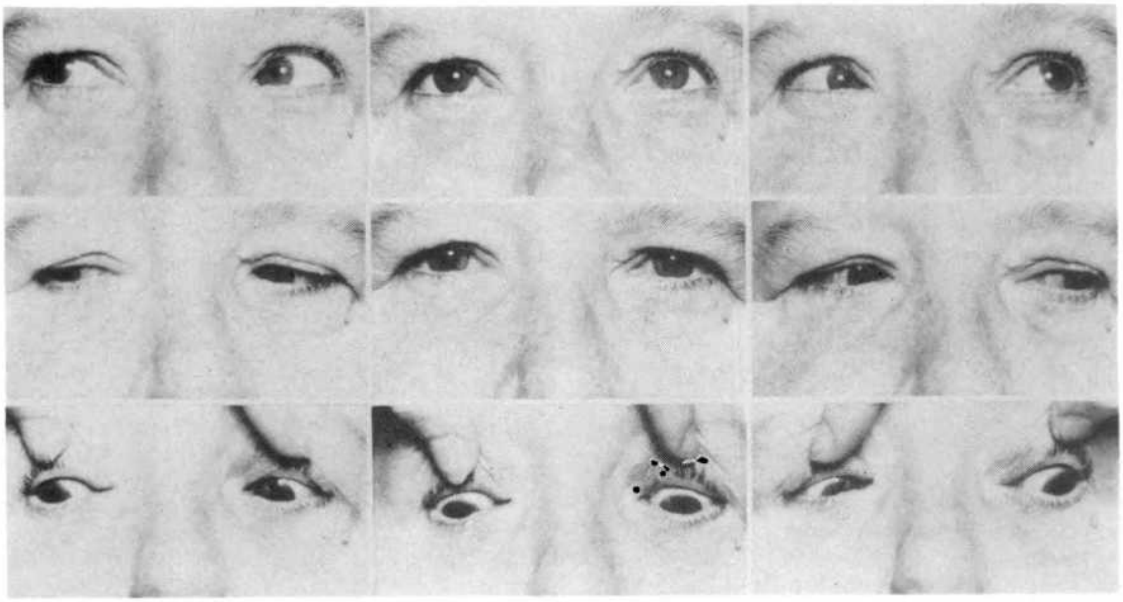

Fig. 2 *Nine positions of gaze showing bilateral Brown's syndrome.*

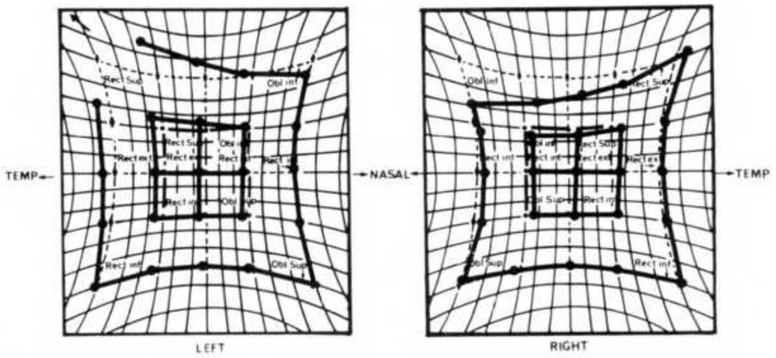

Fig. 3A

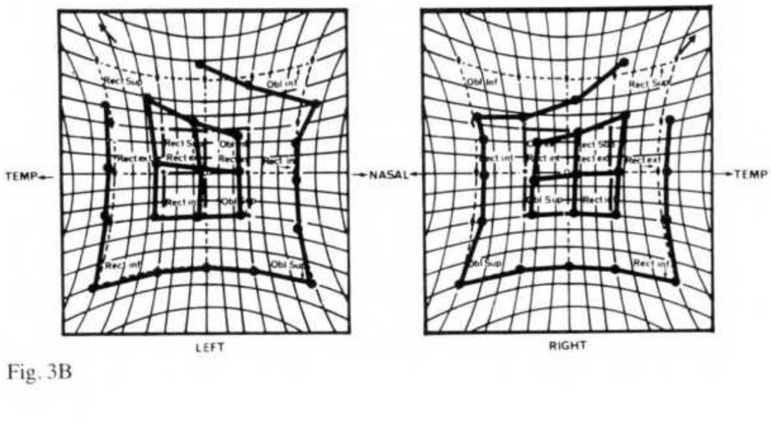

Fig. 3B

Fig. 3 A: *Hess chart demonstrates the apparent underaction of the inferior oblique muscles and overaction of the superior oblique muscles of the bilateral Brown's syndrome. August 1984.* B: *Hess chart shows slight worsening six months later.*

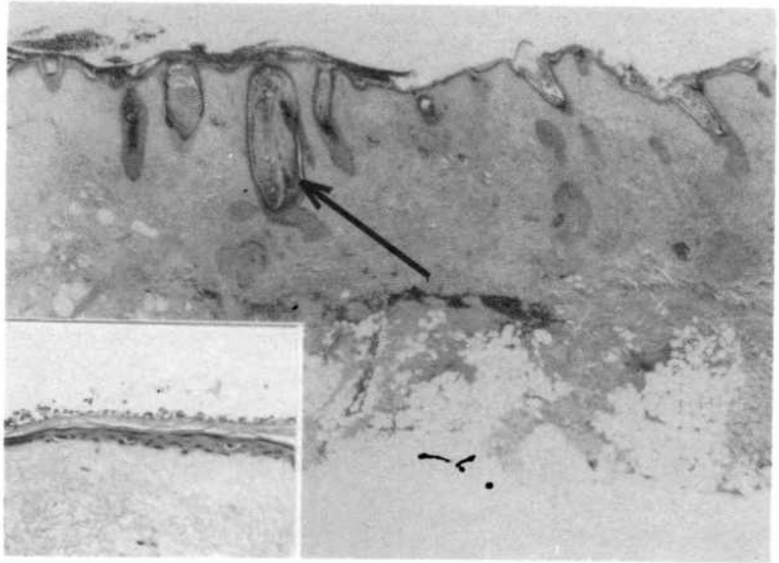

Fig. 4 *Skin biopsy from forehead. At low magnification there is apparent distension of hair follicles by plugs of keratin (arrow) and extension of dermal collagen into subcutaneous fat. At higher magnification (inset) the epidermis can be seen to be atrophic without showing degeneration of the basal layers, and there is oedema and flattening of the papillary dermis. The appearances indicate combined morphoea and lichen sclerosis et atrophicus. H and E, ×17 (inset, H and E, ×67).*

forced duction test confirmed marked limitation of elevation on adduction and slight limitation of elevation in abduction. In the left eye there was slight limitation of elevation in adduction. During the following six months new skin lesions became apparent and existing skin lesions progressed. The diplopia on elevation became more noticeable (Fig. 3B). She continues to be followed up and there have been no further changes of her acquired Brown's syndrome.

HISTOPATHOLOGY

A punch biopsy of the bullous lesion on her right hip had shown haemorrhagic subepidermal bullae, a perivascular chronic inflammatory cell infiltrate, and periadenexal inflammation with thickening of dermal collagen which was of a hyaline appearance. These features indicated a histological diagnosis of morphoea.

Two further skin biopsies were examined: one from the forehead at the margin of the largest (en coup de sabre) lesion and one from a small lesion on the right cheek. Both biopsies were similar in appearance in histological sections (Fig. 4). The epidermis was atrophic and separated from the reticular dermis by an area of oedema within the collagen. There was no evidence of liquefaction of the basal layer of the epidermis. Follicular plugging was observed, and there was fibrosis of the dermis extending into the subdermal fat. A perivascular acute and chronic inflammatory cell infiltrate was seen, particularly in the deeper layers of the dermis. Although there was follicular plugging, the distribution of the inflammatory infiltrate was not consistent with discoid lupus erythematosus. The deep extension of fibrosis, combined with epidermal atrophy, follicular plugging, and oedema of the papillary dermis indicates a histological diagnosis of combined lichen sclerosis et atrophicus and morphoea.

Discussion

In this case of bilateral acquired Brown's syndrome the diplopia preceded the manifestation of the skin lesions and increased in severity as the skin lesions grew in extent. In morphoea the fibrosis is believed to start in the lower dermis,[16] which supports the view that the diplopia was caused by morphoea of the overlying skin.

Ophthalmic problems previously reported to be associated with morphoea are many and various. They include loss of cilia and supracilia, tarsal atrophy, iritis, iridopalpebral atrophy,[17] unilateral glaucoma,[18] heterochromia,[19] atrophy of skin and muscle including extraocular muscle occurring with en coup de sabre lesion,[20 21] perilimbal vascular anomaly,[22] corneal opacity and fundal changes.[23] This patient had loss of cilia and supracilia, raised intraocular pressures, and episcleritis as complications of her morphoea in addition to Brown's syndrome.

Lichen sclerosus et atrophicus has been described as occurring on the eyelid,[24] producing lid notching and ectropion.[25] Combined lichen sclerosus et atrophicus and morphoea is rare[26 27] and is thought to be a manifestation of the same disease process; it tends to behave as morphoea alone and is usually self-limiting or gradually progressive; with no treatment is effective.

The histopathology of skin lesions on the face, clinically similar to those overlying the trochleae, showed the infiltration of deep fibrosis into the subdermal fat which is part of the morphoea component of the combined skin disease. We postulate that bands of fibrosis extended into the perisheath region round the trochlea and mechanically limited the passive movement of the superior oblique tendon in elevation in adduction.

The function of the trochlea has been studied by various authors.[24-28] Helveston *et al.*[28] have shown from light and electron microscopical examination of eight specimens of trochlea that the tendon is separated from the trochlea by an encircling vascular layer and an outer thin bursa-like space The tendon is composed of parallel fibres with low adhesion to each other along their length, so that movement through the trochlea occurs by differential sliding of the fibres in a telescoping fashion, with only the central fibres completing the whole excursion. Excess fluid in this bursa or distension of the vascular sheath is postulated to restrict movement through the trochlea, causing an acquired Brown's syndrome which may be associated with a click

Sevel[29] demonstrated from 54 embryological and fetal specimens the existence of fine trabeculae between the tendon and the trochlea, the persistence of which into adulthood may prevent this sliding movement and limit the excursions of the tendon in the congenital form of Brown's syndrome.

Koorneef[30] considered that the orbital connective tissue and the extraocular muscles functioned as a single anatomical entity. He has demonstrated from histological thick sections of the orbit that the superior oblique tendon has many connective tissue bands with the medial aponeurosis of the levator muscle and also large numbers of septa passing to the globe along the course of the tendon from the trochlea to the posterior surface of the eye. Accordingly, it is not surprising that perisheath scarring in the medial upper quadrant should mechanically limit passive movement of the superior oblique tendon to produce a Brown's syndrome.

Repeated peritrochlear steroid injections have been reported by Beck and Hickling[31] to be effective in cases of Brown's syndrome occurring with rheumatoid arthritis and in acquired cases presumed to be due to acute stenosing tenosynovitis.[32] Peritrochlear injection of steroids was not carried out in this case, as morphoea rarely responds to local infiltration of steroids or systemic treatment. This is probably because there is already established fibrosis in the deep dermis by the time the skin lesions have appeared. In addition this patient was able to avoid troublesome diplopia by adopting a tolerable compensatory head posture.

This case shows that morphoea of the periorbital skin should be added to the list of causes of acquired Brown's syndrome.

We thank Mr Paul Mills for allowing us to report this case and Alison Firth (Orthoptic clinical teacher UHW) for her help, Karen Johnstone (MEH) for the drawings and the Medical Illustration department at UHW for the photographs

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Correspondence

Irradiation and choroidal melanoma

SIR, In their paper questioning whether irradiation is a justifiable treatment for choroidal melanomas Manschot and van Strik[1] base their conclusions on a thesis that has some major internal inconsistencies. They claim that dissemination of choroidal melanoma generally occurs after the tumour has grown to 7 mm or larger, that doubling times of uveal melanomas vary from 30 to 365 days, that death from metastasis occurs 30–40 doubling times after dissemination, and that tumour related deaths within three years after therapy are caused by pre-existing metastases. This is a reiteration of the views expounded a few years earlier by Manschot and van Peperzeel [2]

In his Bowman lecture of 1980 Zimmerman pointed out why those concepts could not be logically used to advocate the need for early enucleation.[3] Using their own views concerning the similarly slow growth rates of the primary and metastatic tumours and their own postulates, formulas, and tumour doubling times, some calculations were made and published as Table II. Reference to that table (reproduced here) shows that various combinations of data that would explain the peak occurrence of tumour deaths from melanomas measuring 15 mm in diameter within the first four postoperative years would require either that the tumours metastasised before they reached 4 mm in diameter, or that the primary tumours grew with such unrealistic rapidity as to give doubling times of 20–25 days. For the same reasons Manschot and van Strik cannot use their concepts to account for the data they presented in their Table 1, indicating no mortality in tumours less than 7 mm in diameter

If, therefore, Manschot and van Strik insist that all tumour deaths occurring within three years after therapy are the result of dissemination prior to treatment, then they must acknowledge that such dissemination must have begun before the tumours had become symptomatic. Quite obviously, if that were the case, any debate concerning whether treatment should be by enucleation or irradiation would be irrelevant

Let us make it clear that these calculations showing that dissemination must have begun when the tumours were minuscule were based entirely on the Manschot—van Peperzeel model,[2] which again provides the basis for the most recent article by Manschot and van Strik.[1] Obviously the model must be flawed and is clearly non-applicable, because early dissemination from tiny tumours is inconsistent with the generally accepted observation that deaths from metastasis are rare when tumours are treated before they have grown larger than 7 mm, as they indicated in their Table 1.

Manschot and van Strik then go on to insist that survival rates for less than four years after therapy are irrelevant in evaluating the efficacy of therapeutic regimens, and that our attention should be focused on survival rates of 10 years or more We on the other hand are much more concerned about the fact that the greatest mortality occurs during the first several years after enucleation.[4-7] The overall 15-year mortality is about 45% after enucleation, but two-thirds of these tumour deaths are within the first five years, with the peak occurring during the second year. Postenucleation mortality patterns remarkably similar to ours that were derived from cases treated in the USA have been reported by Benjamin *et al.*[8] from London and by Jensen from the Danish Registry.[9,10]

This curious mortality pattern, which Manschot and his colleagues have been unable to explain satisfactorily and which they recommend that we neglect by focusing our attention on tumour death rates after 10–15 years is in our

Table II* *Implications of Manschot and van Peperzeel's model based on a melanoma measuring 15 mm at time of enucleation and 36 doubling times (Tds) from initial metastasis to death*

Value of Td (days)	*Years from enucleation to death*	*Tds from enucleation to death**	*Tds from initial metastasis to enucleation**	*Years from initial metastasis to enucleation*	*Size of uveal melanoma when metastasis began (mm)*
200	2	3	33	18	< 0 01
200	4	7	29	16	0 02
200	>15	29	7	4	< 3 5
100	2	7	29	8	< 0 02
100	4	15	21	6	0 12
100	8	30	16	4	3 8
50	2	14	22	3	< 1 2
50	4	30	6	< 1	3 8
50	4 5	33	6	< 0 5	7 5
25	2	29	7	< 0·5	< 3 75
25	2 25	33	3	0 2	7·5
25	2.5	36	0	0	15
20	1	18	18	1	0 24
20	1 5	28	8	0 5	< 2 5
20	2	36	0	0	15

*From Zimmerman [3]

Example. A patient died in the 2nd year after enucleation If the doubling time for his tumour had been 100 days (Row 4), metastasis must have occurred when the primary was less than 02 mm in diameter Row 4 also shows the elapsed interval from metastasis to enucleation would have been 29 doubling times, or 8 years view the major problem It has been the broad experience of ophthalmologists, pathologists, and epidemiologists that deaths from untreated uveal melanomas are most unusual. Yet within the first few years after enucleation an appreciable mortality develops; then 6–7 years after enucleation the slope of the survival curve flattens out to an annual death rate of about 1–2%.

During the past two decades there has been a significant change in attitude concerning the management of uveal melanomas. Once considered to be lesions demanding enucleation as soon as possible after diagnosis, melanomas are now often left untreated until there is documentation that the tumour is growing and producing significant pathological effects on the eye Manschot and others have feared that this change in attitude would significantly increase the tumour death rate, but to date there has been no documentation that this has occurred Returning to the mortality pattern previously described, if as Manschot and his colleagues would have us believe, all tumour deaths within three years of treatment are the result of dissemination that began before treatment, then we would expect to see a similar mortality pattern among patients whose tumours were not diagnosed and treated promptly after they became symptomatic. We have been collecting cases of this type, but have not observed a similar peaking of mortality during the first few years after the untreated tumours became symptomatic

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SIR, Thank you for allowing us the opportunity to reply to the letter by Drs Zimmerman and McLean. It is disappointing that this letter does not address the subject matter of our paper on irradiation of ocular melanoma.[1] Their letter is a reiteration by the same correspondants of a similar submission some eight years ago to another leading journal,[2] in which they criticised a paper by one of us (WAM) and H A van Peperzeel [3] It is probably for this reason that the 1988 letter does not cite any publications after 1980, apart from McLean *et al.* 1982.

Take the serious points in order:

Paragraph 1 ('Sir, in … diameter')· Zimmerman and McLean refer to a Bowman lecture[4] in which Zimmerman argued that our concepts could not be used logically to advocate the need for early enucleation. The correspondents have failed since 1980—also in the 1980 Bowman lecture—to substantiate by decisive arguments that our concepts cannot be used to advocate early enucleation as the only justifiable treatment of choroidal melanoma. They never received any support for their opinion, but have, on the contrary, been contested themselves by especially those authors who have published calculated doubling times of choroidal melanomas.[5,6] Zimmerman and McLean have ignored in their text our reply[7] to their eight-year-old letter and have neglected the paper by Seigel *et al*,[8] who clearly demonstrated the pattern of a peak mortality in the early years after diagnosis in all tumour types studied. According to these authors there was no relationship between the increased risk of death after enucleation and the enucleation, which had also been emphasised in our paper [3]

Paragraph 2 ('If, therefore, . . irrelevant '). We certainly insist that practically all tumour deaths occurring within three years after therapy are the result of dissemination prior to treatment, and that dissemination must have begun before the tumours had become symptomatic in those cases in which no prolonged patient's or doctor's delay had occurred. We find it hard to accept the statement made by Zimmerman and McLean: 'Quite obviously, if that were the case, any debate concerning whether treatment should be enucleation or irradiation would be irrelevant' Enucleation of all eyes harbouring a melanoma of any size saves about 50% of these patients from tumour death Today melanomas are generally detected at a much earlier stage than in former years, and the 10-year survival of 50% has been considerably improved in the meantime. The debate is far from irrelevant, because Zimmerman and McLean imply that irradiated melanomas cannot disseminate after treatment Since fewer than 50% of melanomas studied microscopically after irradiation showed necrosis and 94% contained viable tumour tissue,[9] it seems inevitable that some of the irradiated tumours will continue to shed tumour cell emboli.

Paragraph 3 ('Let us . Table 1')· Our model should be 'obviously clearly non-applicable, because . . deaths from metastases are rare when tumours are treated before they have grown larger than 7 mm' There is no acknowledgment that one of us (WAM) was the first to emphasise[1,10] the critical importance of tumour size in small melanomas in prognosis Analysis of two reports[11,12] on the survival of patients with small enucleated melanomas in the <7 mm and the <10 mm diameter groups revealed that the tumour death rate in the two studies of 7–10 mm tumours was about

35% and 40% compared with nil % in the <7 mm groups. The authors of these two reports[11,12] calculated 22·7% and 14·3% in the <10 mm groups, because they had not specially determined the death rates in the 7–<10 mm groups. Our model is, contrary to the opinion of Zimmerman *et al.*, fully applicable to the high tumour-related death rates in the 7–<10 mm group, because only a very small percentage of melanomas are enucleated before they have grown larger than 7 mm and because calculated doubling times of 36 out of 39 uveal melanomas[5,6,13,14] appeared to vary from 60 to 540 days[14] or even 900 days.[5]

Paragraph 4 ('Manschot .. Danish registry'): Zimmerman and McLean criticise our emphasis on survival data based on a 10-year follow-up. It has been emphasised above that the calculated doubling time of 36 out of 39 uveal melanomas was more than 60 days. Death by metastasis occurs 35–40 doubling times after dissemination [3] Thus we know that even survival rates up to more than six years after treatment (35×60 days=6·1 years) will be irrelevant in evaluating or comparing the efficacy of therapeutic regimens, because more than 90% of metastatic deaths must be due to dissemination prior to treatment.

Paragraph 5 ('This curious . 1–2%'): This curious pattern of peak mortality has been repeatedly and exhaustively explained by us[1,2,15] and others.[8] We regret that Zimmerman and McLean find these explanations unsatisfactory, but we are consoled by the absence of any accurate basis for their criticism. We also have never recommended that this curious pattern be ignored, but have stressed that it must be accepted.[3,15] The major problem which Zimmerman and McLean refer to in this paragraph would have been solved had they cited recent literature on doubling times.[5,6,13,14] We are further perplexed, however, to read the unsubstantiated statement that 'It has been the broad experience of ophthalmologists, pathologists, and epidemiologists [all anonymous] that deaths from untreated uveal melanomas are most unusual' It is noteworthy that Zimmerman and McLean had reported in 1979[16] that they had collected 80 proved cases in which untreated uveal melanomas had metastasised They then also acknowledged that much pertinent information is lost, because the cases usually do not come to the attention of ophthalmologists or ophthalmic pathologists.

Paragraph 6 ('During .. symptomatic'): For more than 15 years, irradiation of uveal melanomas has been a regular practice in many clinics in the USA and in Europe. So far only one clinic has reported survival rates and the functional results in *all* the treated patients after a mean follow-up period of 10 years [17] Survival figures for 27 patients treated by enucleation were compared with those of 21 patients who had been treated with cobalt-60 episcleral plaques in the same period. Of the enucleated patients 22% had died from metastases against 57% of the irradiated patients. The median survival after enucleation was 10 years, after irradiation it was 3·8 years. No other clinics have published the survival figures for all the treated cases for a follow-up period of 10 years or more. We are apprehensive that the ophthalmological community will have to wait for a long time before definitive 10-year survival statistics for all patients treated by irradiation are made available by the majority of the radio-oncology clinics A collection of anonymous, non-specified cases, as mentioned in the last sentence of the letter by Zimmerman *et al.*, is not very helpful to convince doubting colleagues

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TABLE OF CONTENTS

ORIGINAL ARTICLES

- A proposed mild type of acute retinal necrosis syndrome Toshihiko Matsuo, Tadashi Nakayama, Tetsuro Koyama, Masaya Koyama, and Nobuhiko Matsuo
- Asymmetric retinopathy in patients with diabetes mellitus David J. Browning, Harry W Flynn, Jr, and George W. Blankenship
- Detection of the carrier state of X-linked retinoschisis Geoffrey B Arden, Michael B. Gorin, Philip J Polkinghorne, Marcelle Jay, and Alan C. Bird
- Detection of lymphocytes in the vitreous gel of patients with retinitis pigmentosa David A Newsome and Ronald G. Michels
- A familial study of the inheritance of HLA-B27-positive acute anterior uveitis P J F. M Derhaag, A Linssen, N. Broekema, L. P de Waal, and T E W Feltkamp
- Immunopathologic study of Vogt-Koyanagi-Harada syndrome Chi-Chao Chan, Alan G Palestine, Toichiro Kuwabara, and Robert B Nussenblatt
- Magnetic resonance imaging of nonmetallic orbital foreign bodies W. Bruce Wilson, James N Dreisbach, Daniel E Lattin, and John C. Stears
- Transient proliferative diabetic retinopathy during intensified insulin treatment Ellen F Rosenlund, Kirsti Haakens, Olaf Brinchmann-Hansen, Knut Dahl-Jorgensen, and Kristian F. Hanssen
- Corneal fistulas and their management Mark J Mannis, James Ruben, and Linda Wedemeyer
- Infected vs sterile corneal infiltrates in contact lens wearers Raymond M Stein, Thomas E Clinch, Elisabeth J Cohen, Gail L Genvert, Juan J Arentsen, and Peter R Laibson
- The effect of suture removal on postkeratoplasty astigmatism Perry S Binder
- A study of race matching between donor and recipient in corneal transplantation David C Musch, Roger F Meyer, Alan Sugar, and H Kaz Soong
- The effect of radial keratotomy on contrast sensitivity M M Krasnov, S E. Avetisov, N V Makashova, and V R. Mamikonian
- Necrotizing keratitis caused by Capnocytophaga ochracea David G Heidemann, Stephen C. Pflugfelder, Jan Kronish, Eduardo C. Alfonso, Steven P. Dunn, and Saul Ullman
- Mycobacterium fortuitum keratitis Pravin U Dugel, Gary N. Holland, Harry H Brown, Thomas H. Pettit, John D Hofbauer, Kenneth B Simons, Henry Ullman, Patricia E Bath, and Robert Y Foos
- Toxic endothelial degeneration in ocular surface disease treated with topical medications containing benzalkonium chloride Michael A Lemp and Lorenz E Zimmerman
- Use of an angiotensin converting enzyme inhibitor in ocular hypertension and primary open-angle glaucoma William H Constad, Philip Fiore, Cesar Samson, and Alfonse A Cinotti
- Comparison of intraocular pressure measurements with the Oculab Tono-Pen vs manometry in humans shortly after death Volker Hessemer, Ralf Roessler, and Karl W. Jacobi

EDITORIAL

- The Leslie Dane gold medal Robert C. Drews

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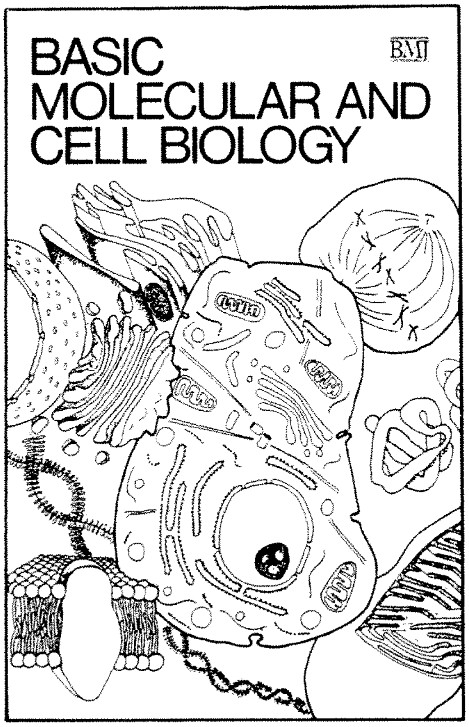

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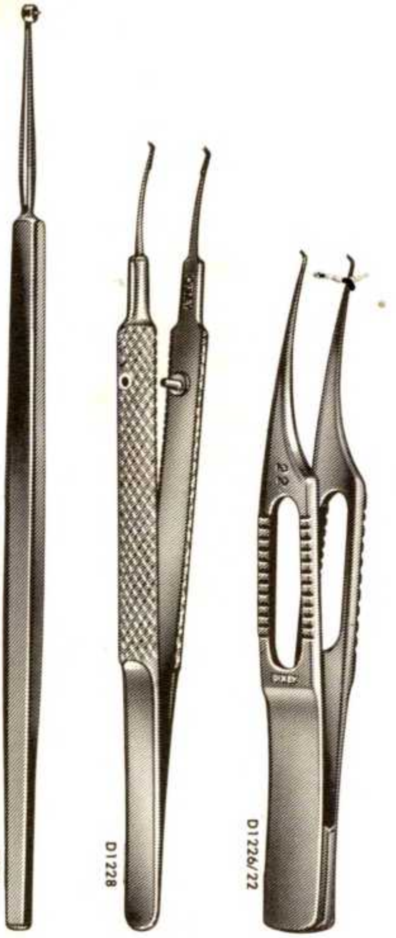

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British Journal of Ophthalmology July 1988 Vol. 72 No. 7

Contents

Changing patterns of early complications in cataract surgery with new techniques: a surgical audit J F ACHESON, J D MCHUGH, AND M G FALCON *page* 481

The Ciapryna coaxial cannula R V PEARSON AND J D JAGGER *page* 485

Control of astigmatism in cataract surgery NICHOLAS A P BROWN AND JOHN M SPARROW *page* 487

Cobalt plaque versus enucleation for uveal melanoma: comparison of survival rates KIMBERLEY S ADAMS, DAVID H ABRAMSON, ROBERT M ELLSWORTH, BARRETT G HAIK, MICHAEL BEDFORD, SAMUEL PACKER, JOHANNA SEDDON, DANIEL ALBERT, AND LELA POLIVOGIANIS *page* 494

Intravitreal injection of fibroblasts: the pathological effects on the ocular tissues of the rabbit following an intravitreal injection of autologous skin fibroblasts CATHRYN A HITCHINS AND IAN GRIERSON *page* 498

Perforating eye injuries caused by darts M D COLE AND D SMERDON *page* 511

The one-and-a-half syndrome. Clinical correlation with a pontine lesion demonstrated by nuclear magnetic resonance imaging in a case of multiple sclerosis C N MARTYN AND D KEAN *page* 515

Single-dose cefotaxime intramuscularly cures gonococcal ophthalmia neonatorum PHILIPPE LEPAGE, JOS BOGAERTS, PHILIPPE KESTELYN, AND ANDRÉ MEHEUS *page* 518

Intravenous and intraocular ganciclovir for CMV retinitis in patients with AIDS or chemotherapeutic immunosuppression GEORGE L DAIKOS, JOSE PULIDO, SHASHI B KATHPALIA, AND GEORGE GEE JACKSON *page* 521

Treatment of cytomegalovirus retinitis with ganciclovir (9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine (BW B759U)) JUAN ORELLANA, STEVEN A TEICH, JACQUELINE S WINTERKORN, USHA MATHUR-WAGH, SANDRA HANDWERGER, HARAN SCHLAMM, STEPHEN C MALAMUD, STANLEY R YANCOVITZ, DONNA M CEDERBERG, AND DONNA S MILDVAN *page* 525

Severe herpetic keratitis. I: Prevalence of visual impairment in a clinic population CHARLES M P CLAOUÉ, MITCHEL J MÉNAGE, AND DAVID L EASTY *page* 530

Pattern visual evoked potentials in hyperthyroidism K W MITCHELL, C M WOOD, AND J W HOWE *page* 534

Central compaction in the process of lens growth as indicated by lamellar cataract NICHOLAS A P BROWN, JOHN M SPARROW, AND ANTHONY J BRON *page* 538

A morphometric study of endothelial cells of human corneas stored in MK media and warmed at 37°C DAVID S ROOTMAN, SYED M HASANY, AND PRASANTA K BASU *page* 545

Lamellar macular hole associated with idiopathic juxtafoveolar telangiectasia B PATEL, J DUVALL, AND A B TULLO *page* 550

Acquired Brown's syndrome in a patient with combined lichen sclerosus et atrophicus and morphoea J OLVER AND P LAIDLER *page* 552

Correspondence *page* 558

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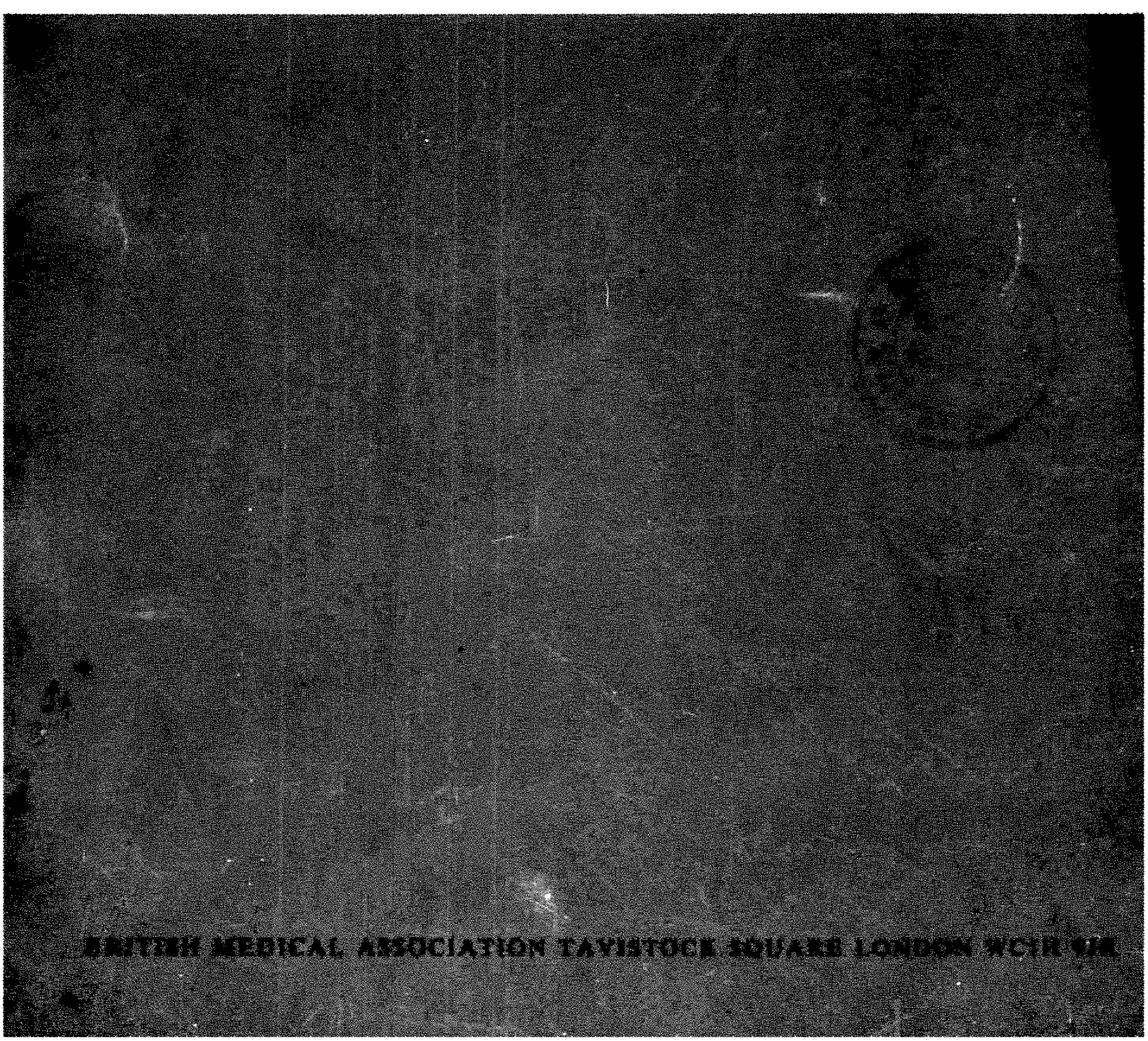

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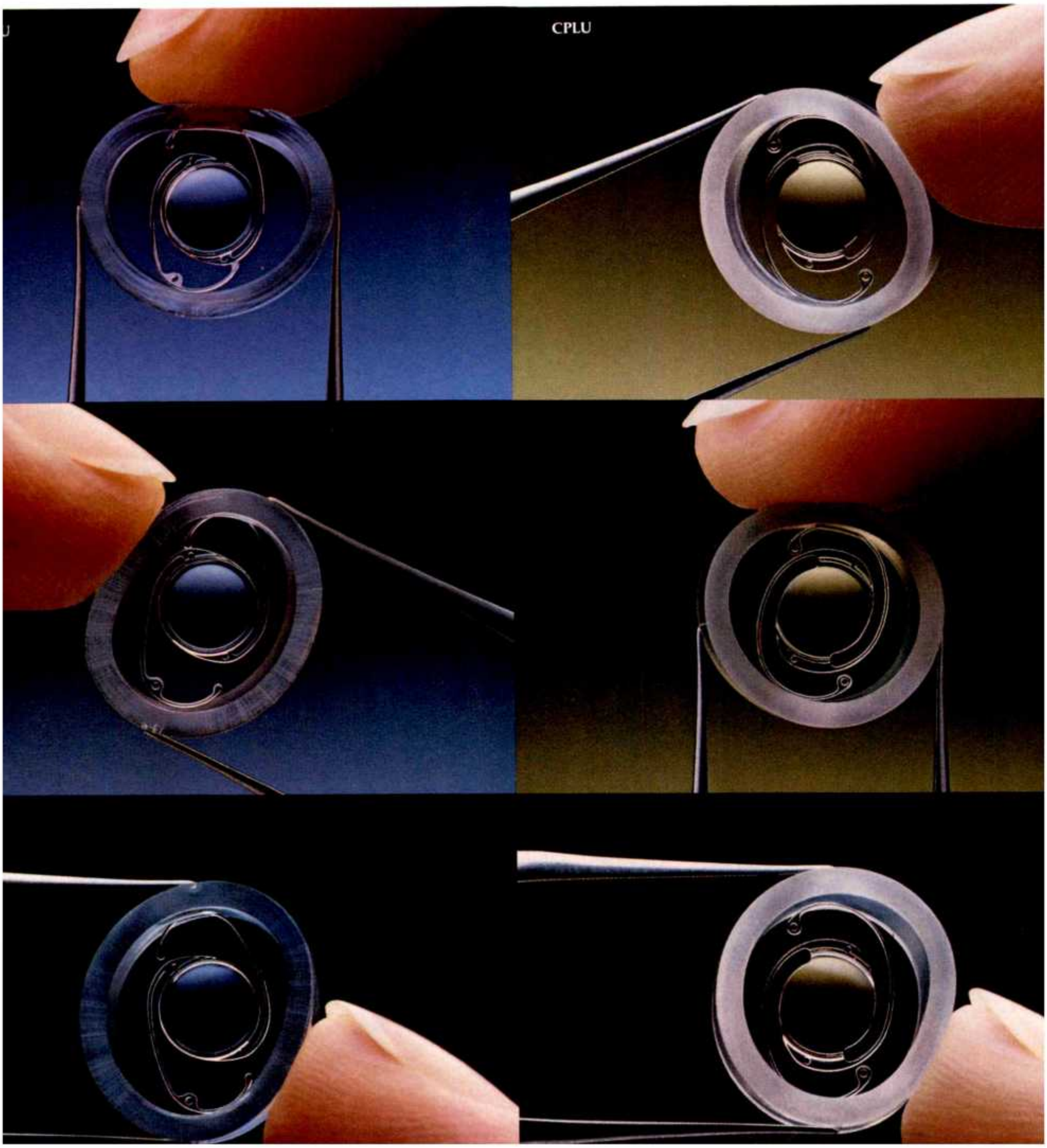

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Effect of single-dose invermectin therapy on human *Onchocerca volvulus* infection with onchocercal ocular involvement

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SUMMARY Ivermectin has shown promise as a potentially safe and effective microfilaricidal drug for the treatment of onchocerciasis. Several limited studies have shown it to have fewer side effects, especially ocular complications, than the currently available drug, diethylcarbamazine. The detailed ocular findings in 200 moderately to heavily infected Liberians who were enrolled in a safety and dose-finding study are presented. They received either 0, 100, 150, or 200 μg/kg of ivermectin and were followed up for 12 months. In clinical studies so far carried out ivermectin in a dose of 100, 150, or 200 μg/kg has not been associated with any major adverse reactions nor were there any sight-threatening effects even in the presence of severe ocular disease. Each of these doses significantly reduced the ocular microfilaria load for at least 12 months when compared with either the placebo ($p<0.05$) or pretreatment values ($p<0.001$). However, the 100 and 150 μg/kg doses caused fewer minor side effects than the higher dose. These results confirm that ivermectin in a single oral dose may be a safe and effective microfilaricidal drug for the treatment of onchocerciasis and that it appears to be free of major ocular side effects.

No appropriate treatment is available for widespread use against onchocerciasis. The two drugs used, diethylcarbamazine (DEC) and suramin, are associated with severe systemic and ocular side effects. The ocular side effects of DEC are well known and include permanent sight-threatening changes and sometimes blindness.[1-6] DEC is therefore recommended only for patients with severe disease, especially those whose sight is severely threatened without treatment.[7,8] Suramin, which is inherently toxic,[9] also causes similar ocular changes.[10] Invermectin, a semisynthetic macrocyclic lactone widely used in veterinary medicine, shows promise as a microfilaricidal drug that has been better tolerated than DEC and has fewer ocular complications in the studies conducted so far.[11-18]

Studies of invermectin treatment in man that have been reported so far are limited to fewer than 100 patients, most of whom had either relatively mild disease or incomplete follow-up. We report here the detailed ocular findings of a double masked study of dosage and efficacy in which 200 patients with moderate to severe onchocerciasis were treated with one of three different doses of invermectin or placebo. The detailed systemic findings in this group of patients are being reported separately.[19]

Subjects and methods

SUBJECTS

Eight hundred patients, aged 12–60 years, were screened clinically and parasitologically. The 200

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patients with heaviest infection by microfilaria skin count who were otherwise apparently healthy and who had given consent were selected for inclusion in this study. All patients had screening skin-snip microfilaria counts of greater than 15 microfilaria per mg of skin. Pregnant and lactating females and any subject who had received an antifilaricidal within one year were excluded.[18] They were residents of the Liberian Agricultural Company rubber plantation in Grand Bassa County, Liberia, an area hyperendemic for the rain forest type of onchocerciasis.

CLINICAL EVALUATION

The patients underwent detailed ocular, physical, and parasitological examination before the start of treatment.[19] The ocular examination included the testing of visual acuity with an illiterate E chart and visual fields with a clear dome perimeter using a 2 mm fibreoptic target (Goodlite Company, Forest Park, Illinois).

The anterior chamber and cornea were examined with a Topcon SL5D slit-lamp at 25× after the subjects were placed in the head down position for at least two minutes. The microfilariae in the cornea and the anterior chamber of each eye were counted. Limbitis was diagnosed by the presence of limbal vessel dilatation, limbal oedema, and white globular opacities, and each sign was graded as absent, mild, moderate, or severe. Anterior uveitis was diagnosed by the presence of anterior chamber cells and flare; each sign was graded as absent, mild, moderate, or severe. Sclerosing keratitis was graded according to the presence of limbal haze, the extent of characteristic corneal involvement starting in the nasal or temporal periphery, being confluent inferiorly, or covering the pupil. Intraocular pressure was measured by applanation tonometry.

The fundus was examined by direct and indirect ophthalmoscopy after pupil dilatation with 1% tropicamide and 10% phenylephrine hydrochloride. Fundus photography was performed with a Topcon FE fundus camera; the photographs were graded in a masked fashion with the patient's identity, treatment, and date of examination obscured. These photographs were graded for the presence and extent of intraretinal deposits, intraretinal pigment (IRP), atrophy of the retinal pigment epithelium (RPEA), retinitis, haemorrhage, optic neuropathy, and subretinal fibrosis.[17] Intraretinal deposits are either small white or glistening deposits found in the neuroretina. They could be clearly distinguished in stereo photographs from drusen, which occur at the level of the retinal pigment epithelium. They had a different appearance from intraretinal microfilariae and in our experience do not occur in people living outside areas where onchocerciasis is endemic.

After treatment the detailed ocular examination was repeated at day 3, and at three, six, and 12 months, physical and parasitological examinations were also repeated at these times. In order to quantify the ocular changes due to onchocerciasis and due to therapy an ocular reaction index was calculated.[20] This index is based on the intraocular microfilaria load and the severity of punctate keratitis, limbitis, and anterior uveitis.

All subjects were admitted to hospital during the first four days of the study One hundred and thirty-two patients attended all follow-up examinations. The patients that missed one or more follow-up examinations included eight from the 100 μg/kg, 17 from the 150 μg/kg, 16 from the 200 μg/kg ivermectin groups, and 17 from the placebo group. There were 177 subjects present at three months, 162 at six months, and 176 at 12 months. At 12 months all patients not examined were accounted for as follows: 14 had moved to the interior of the country; six had moved to urban areas and could not be found; the whereabouts of one was unknown; and two refused examination. One patient in the 150 μg/kg group died of undetermined causes between the six- and 12-month examination.

TREATMENT PROTOCOL

Subjects were randomly assigned to receive either 0 (placebo), 100, 150, or 200 μg/kg of ivermectin. The dosage was adjusted for weight, with 5 kg increments. The drug was provided in coded packages containing five identical capsules; each patient was treated individually and closely observed to ensure compliance. Additional medication was available on demand and included aspirin for pain or fever and antihistamine for pruritus or insomnia.

DATA ANALYSIS

Data were gathered in a double-masked fashion and entered for computer analysis prior to breaking the treatment code at six months. The patients were examined at 12 months without reference to the treatment code. Statistical analyses were based on analysis of covariance (to adjust for differences at baseline), with the two-tailed t test for multiple comparisons[21] when means for treatment were compared. In addition the mean differences between groups over time were compared by simple t test for independent samples. Other analyses were performed with Student's t test or Fisher's exact test. The data analysis to be presented was performed on data available for all those patients present at an examination, regardless or their presence at other examinations. Restricting the analysis to only those patients present at every examination (132 or 66%) did not alter the findings.

Results

PRETREATMENT FINDINGS

Random assignment of the subjects into four groups resulted in similar distributions with regard to age, skin microfilaria count, and ocular findings (Table 1). Similarly, weight, number of palpable onchocercal nodules, and skin changes due to onchocerciasis were also evenly distributed.[15]

Thirty-two patients entered the study with visual acuity in one or both eyes of 6/12 or less. Of these, 17 had visual impairment (vision of less than 6/18 in the worse eye). Eight subjects had abnormal visual fields. Their distribution was likewise similar among the treatment groups. Four patients, two in the 100 and one each in the 150 and 200 μg/kg groups, had unilateral optic atrophy.

One patient, a 13-year-old girl in the 200 μg/kg group, had active retinitis and optic neuritis in her only seeing eye, with severe bilateral anterior uveitis and raised intraocular pressure (34 mmH in each eye). This was associated with a massive intraocular microfilaria load (over 100 microfilariae in each anterior chamber). No evidence for other causes of severe intraocular inflammation, such as old toxoplasmosis lesions, could be seen.

CHANGES AFTER THERAPY

The mean skin microfilaria density in the three invermectin treatment groups was significantly reduced at all follow-up examinations in comparison with the placebo group (p<0·01, Table 2). The rapid lowering of skin microfilariae in the first three days after treatment was associated with only mild systemic reactions.[illegible]

Table 1 *Pretreatment characteristics and prevalence of ocular findings*

Finding	*Ivermectin treatment groups*			
	Placebo (n=48)	*100 μg/kg (n=49)*	*150 μg/kg (n=52)*	*200 μg/kg (n=51)*
Mean age (years)	30·5	29·3	29·3	30·3
Microfilaria skin counts (geometric mean, mf/mg skin)	21·0	17·9	21·2	20·8
Punctate keratitis	21* (43·8%)	15 (30·6%)	21 (40·4%)	22 (43·1%)
Microfilariae in cornea	16 (33·3%)	8 (16·3%)	15 (28·8%)	14 (27·5%)
Microfilariae in anterior chamber	26 (54·2%)	19 (38·8%)	27 (51·9%)	24 (47·1%)
Anterior uveitis	0 (0·0%)	2 (4·1%)	1 (1·9%)	1 (2·0%)
Limbitis	5 (10·4%)	6 (12·2%)	5 (9·6%)	7 (13·7%)
Sclerosing keratitis	1 (2·1%)	1 (2·0%)	2 (3·8%)	3 (5·9%)

*Number affected (percentage).

Table 2 *Microfilaria skin densities before and after treatment*

	Microfilaria skin count			
	Placebo (n=48)	*100 μg/kg (n=49)*	*150 μg/kg (n=52)*	*200 μg/kg (n=51)*
Pretreatment	21·0	17·9	21·2	20·8
3 day	17·7	7·0	7·00	4·3
3 months	16·5	0·93	0·65	0·55
6 months	15·6	1·8	1·7	1·3
1 year	13·0	3·1	3·5	3·6

*Geometric mean for all those present at an examination (mf/mg skin) All treatment groups had significant reduction in microfilaria densities at every interval compared to both placebo and to pretreatment levels (p<0·01)

All patients in the ivermectin groups either retained the same visual acuity or improved, but one patient in the placebo group lost some vision in one eye (6/6 to 6/9) when tested at three and 12 months. No cause could be ascribed to this loss of vision. No patient suffered further loss of visual field at any of the follow-up examinations The 13-year-old girl with active retinitis and neuritis at baseline was treated with intensive topical anti-inflammatory and pressure-lowering drugs in addition to ivermectin. She regained visual field, which enlarged from 10° at baseline to 20° at three months There was no progression of optic atrophy in any patient in either the ivermectin or the placebo treated groups, and no new cases of optic neuritis or optic atrophy were seen at any follow-up examination.

The number of microfilariae in the anterior chamber in all treatment groups fell rapidly during the three days following treatment. At three months the difference between the ivermectin treated groups and the placebo group was significant, and it remained significant at the six- and 12-month examinations (p<0·05, Fig. 1). The motility of microfilariae in the anterior chamber was observed to be abnormal for the first three days after ivermectin treatment. This abnormal motility consisted of a characteristic extended configuration, periodic immobility, and an occasional unusual motion in which the microfilariae bent only in the middle, suggestive of a spastic paralysis.

The number of corneal microfilariae in all treatment groups tended to increase by day 3 but had significantly decreased in the ivermectin treated groups at three months in comparison to the placebo group (p<0·01). As with the microfilariae counts in the skin, there was a gradual increase in the number of corneal microfilariae in the ivermectin treated groups between both the three- and six-month

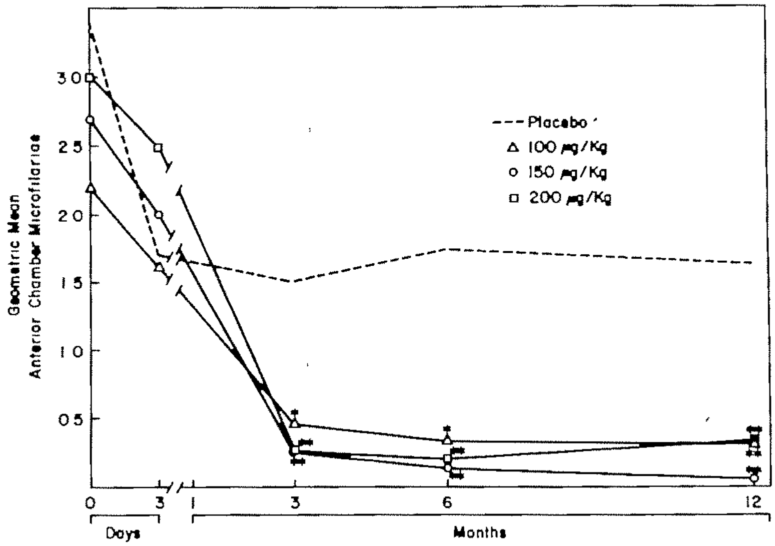

Fig 1 *Geometric mean number of microfilariae in anterior chamber in each treatment group. Asterisks indicate counts significantly different from those in placebo group (single asterisks, p<0·05, double asterisks, p<0·01 (t test))*

examinations and the twelve-month examination. Though not statistically significant, this was more marked in the 200 µg/kg group (Fig. 2). Similar changes were seen in the number of punctate corneal opacities; the 200 µg/kg group showed a small decrease at day three and a more marked (though not statistically significant) increase than the other invermectin groups at both the six- and 12-month examinations (Fig. 3).

In all three ivermectin groups there was a significant decrease in the ocular reaction index in comparison with the placebo group at three, six, and 12 months. There was no significant difference between the three ivermectin groups (Fig. 4).

Chorioretinal abnormalities were noted before and after treatment in patients in all treatment groups (Table 3). Patients were classified by their worse eye. In all instances the chorioretinal changes after treatment were noted to have occurred between the three- and 12-month examination. There was no change in the amount or distribution of IRP in patients with IRP from the ivermectin groups except in one patient in the 100 µg/kg group, in whom progressive IRP clumping was noted (Figs. 5A, B). All those with

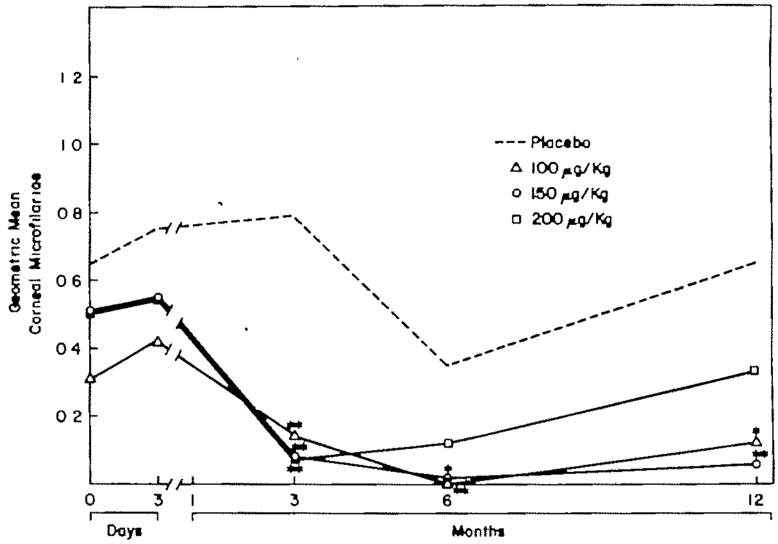

Fig. 2 *Geometric mean number of corneal microfilariae in each treatment group. Asterisks indicate counts significantly different than those in placebo group (single asterisks, p<0·05, double asterisks, p<0·01 (t test)).*

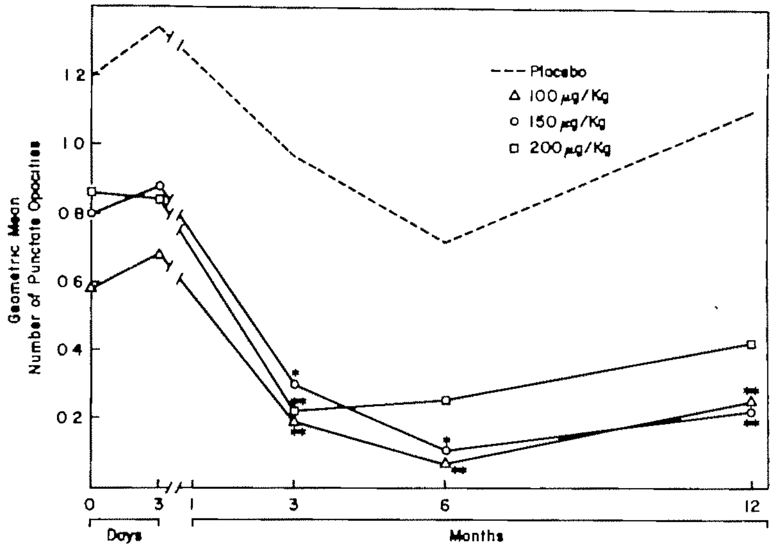

Fig 3 *Geometric mean number of punctate corneal opacities in each treatment group. Asterisks indicate counts significantly different from those in placebo group (single asterisks, $p<0{\cdot}05$; double asterisks, $p<0{\cdot}01$ (t test))*

RPEA in the ivermectin-treated groups remained unchanged (Fig. 6). In contrast, in the placebo group patients with either IRP or RPEA showed progression in 18·2% (four patients) and 23·1% (three patients) of cases respectively. Of patients initially without RPEA none of the ivermectin and 11·4% (four patients) of the placebo patients developed these changes. Nineteen patients with normal fundi before treatment developed retinal deposits, and they were from all four treatment groups. The proportion of patients who developed retinal deposits in the placebo group (seven patients) was significantly greater than that (one patient) in the 200 μg/kg group ($p<0{\cdot}05$). In two patients—a placebo patient and one from the 200 μg/kg group—with pre-existing retinal deposits the number of deposits decreased after treatment.

The one patient with active retinitis and optic neuritis from the 200 μg/kg group (the 13-year-old girl mentioned above) showed some improvement clinically when seen at three days and three months, after which she was lost to further follow-up. One patient in the placebo group had a small area of mild retinitis which remained unchanged throughout the

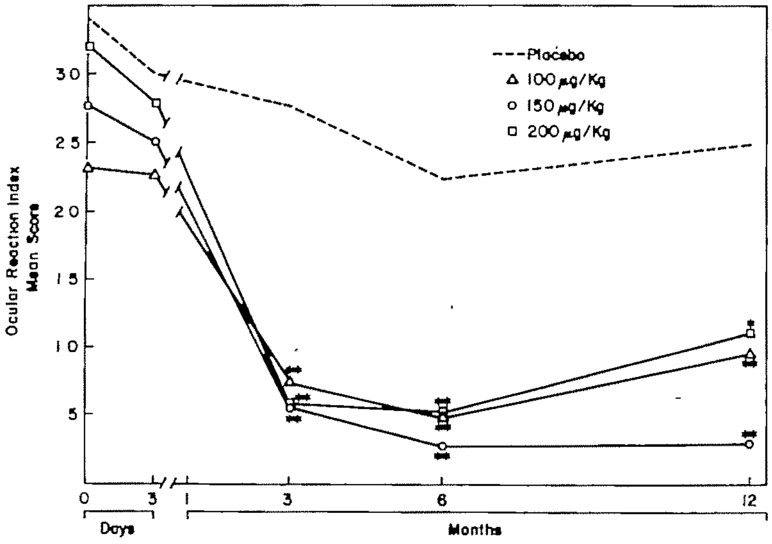

Fig. 4 *Ocular reaction index in each treatment group Asterisks indicate scores significantly different from those in placebo group (single asterisks, $p<0{\cdot}05$, double asterisks, $p<0{\cdot}01$ (t test))*

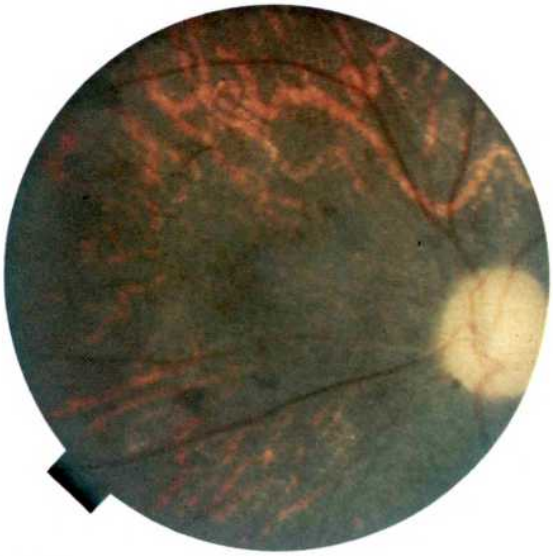

Fig. 5A

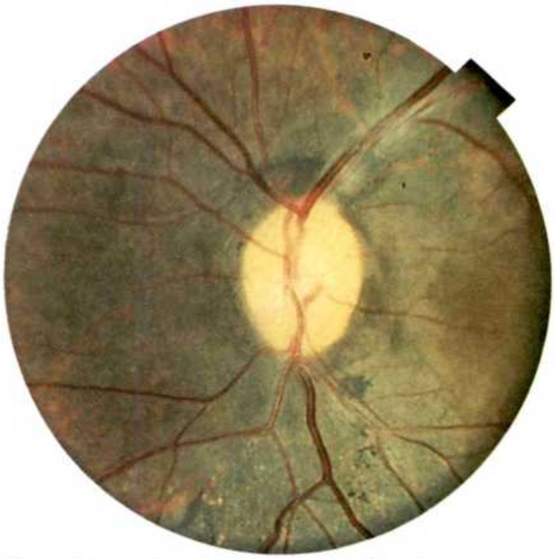

Fig. 6 *Fundus photograph of 19-year-old male patient in the 100 µg/kg group showing retinal pigment epithelial atrophy and white retinal deposits (arrows below disc). Note also intraretinal pigment clumping superonasal to disc.*

study (Fig. 7). A retinal haemorrhage appeared at three months in a placebo patient but had resolved by the six-month assessment (Fig. 8), while a small paramacular area of active retinitis in another patient on placebo remained unchanged during the study.

Discussion

This report presents the detailed ocular findings in a double-masked study of the safety and dosage of ivermectin comparing three different doses with

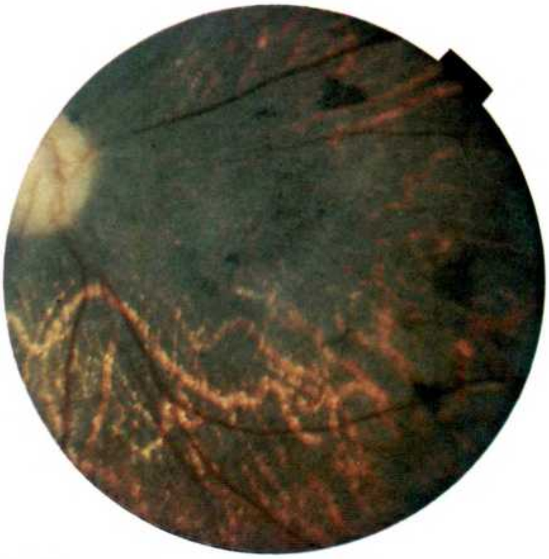

Fig. 5B

Fig. 5 *Fundus photograph of 28-year-old female patient in the 100 µg/kg group before treatment* (A) *and six months after treatment* (B) *in whom there was progressive intraretinal pigment clumping.*

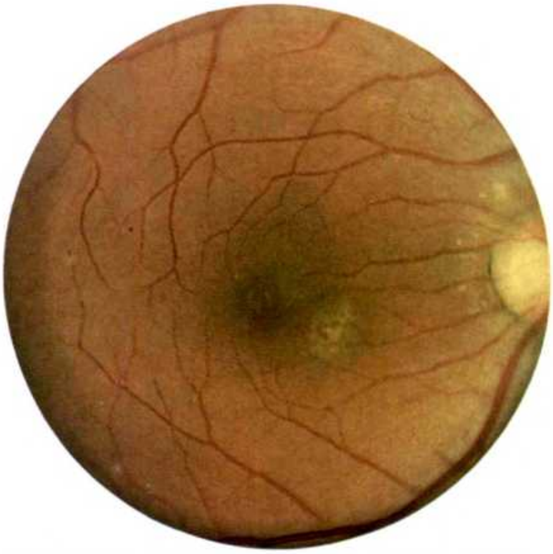

Fig. 7 *Fundus photograph of a 48-year-old male placebo patient who received placebo showing a small area of mild retinitis which did not progress during the study.*

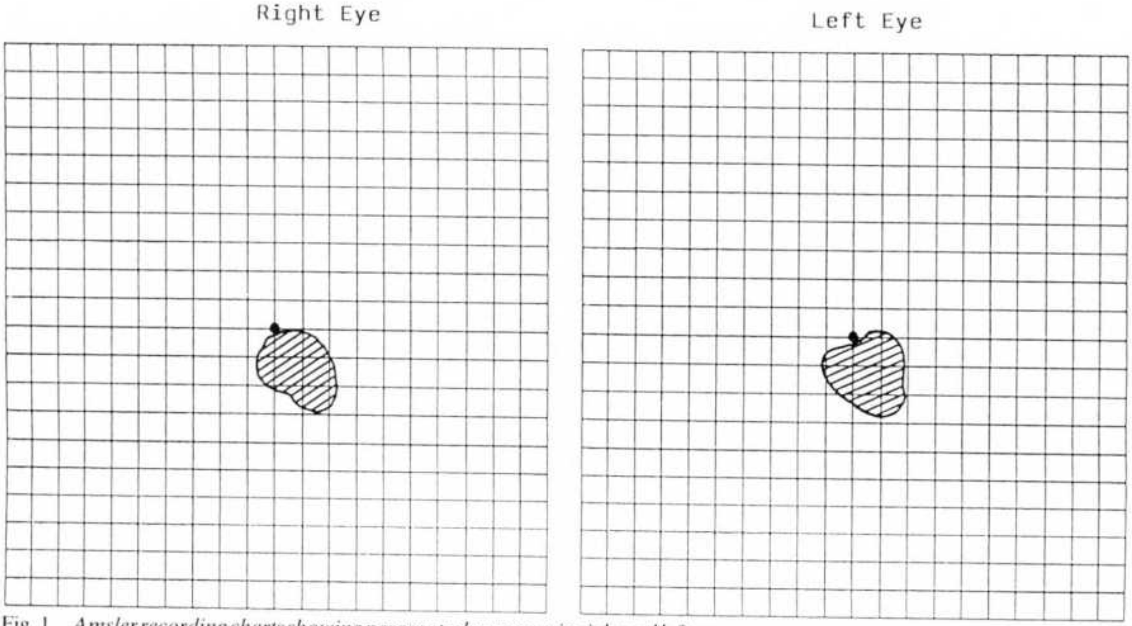

Fig. 1 *Amsler recording charts showing paracentral scotomas in right and left eyes.*

bright spot near the centre of his vision. He presented to his general practitioner and was referred on to hospital the following morning, still complaining of a positive scotoma affecting the lower part of his central field in both eyes. This was plotted by the patient on an Amsler grid at 30 cm (Fig. 1). A slight gritty sensation in both eyes was admitted to only on direct questioning. Unaided visual acuity was

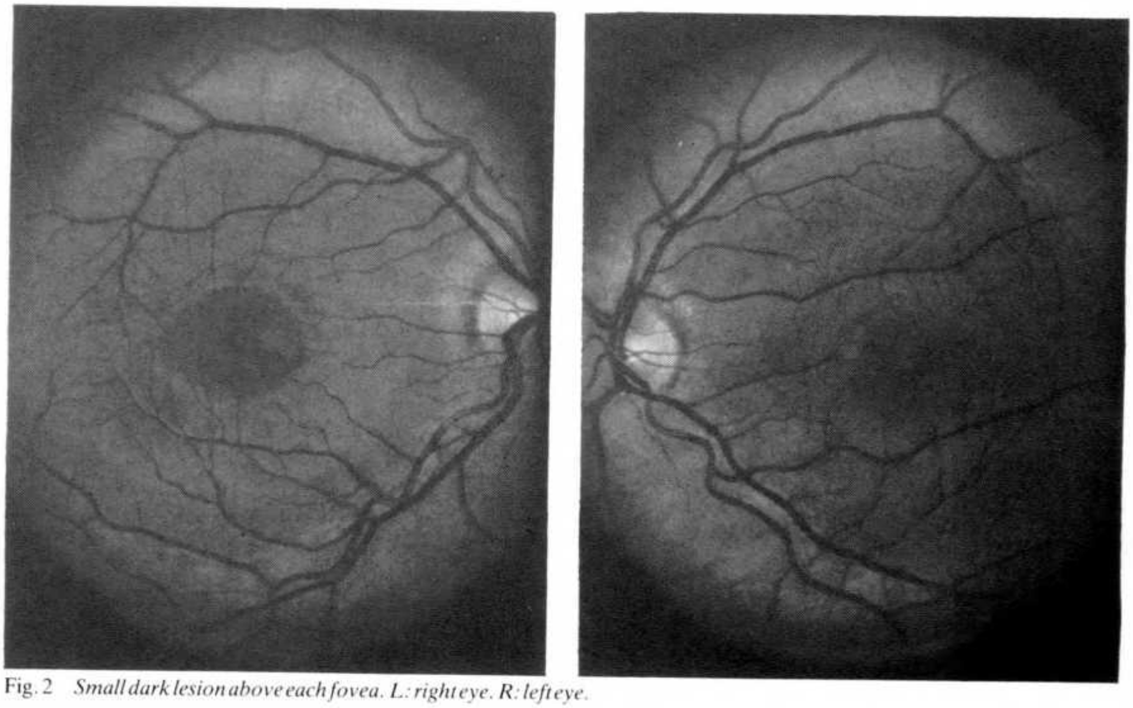

Fig. 2 *Small dark lesion above each fovea. L: right eye. R: left eye.*

recorded as 6/5 in both eyes. Minimal, punctate corneal fluorescein staining was seen on each eye. Retinal examination revealed a triangular, oedematous lesion approximately 0·1 mm in size just above and to the patient's left of each fovea (Fig. 2).

One week later the patient's condition was reviewed. At that time he was symptom free and the retinal lesions were no longer visible. Octopus perimetery (program 34) and fluorescein angiograms of both fundi were normal.

CASE 2

A 39-year-old Asian self-employed motor mechanic presented to the hospital casualty department in the early hours of the morning complaining of painful red eyes, photophobia, and blurred vision. The previous afternoon he had been welding a car body with a MIG welder. It was used underneath the car in poor light, where it was not possible to see through the darkened glass of the protective visor. The patient admitted to 'occasionally' looking round the side of the visor 'for never more than a few seconds' until the arc was struck; enough light would then be produced to enable him to see through the glass filter and allow the visor to be used in the correct manner. The inert gas used was a mixture of argon 75% and carbon dioxide 25%. The arc was formed with 0·6 mm coppered steel wire, and the car body parts were of mild steel. He was inexperienced at welding and had used the machine five or six times, with a total welding time of less than five hours in the previous seven months. He had never received any formal welding training nor had he done any other arc welding.

He was treated with topical antibiotic drops and eye padding. Seen in the eye department later that morning he complained of blurred vision and dark spots in both eyes; the eyes were still painful and photophobic. His corrected visual acuity was 6/7·5 in the right and 6/9 in the left eye. His conjunctivas were hyperaemic, and on slit-lamp examination both corneas showed fine, superficial, punctate fluorescein staining in the areas exposed by the palpebral fissures. Facial ultraviolet erythema was not noted. Examination of the fundi revealed two discrete circular brown coloured lesions in each eye. The lesions were located rather symmetrically temporal to either fovea. The larger was over half a disc diameter in size, the other a third of a disc diameter in size in both eyes; each lesion contained a concentric ring. The smaller lesion in the left eye was less marked than the other lesions (Fig. 3).

One week later the patient was symptom free and his corrected visual acuity had improved to 6/6 in both eyes. Fundus fluorescein angiograms revealed hyperfluorescent areas in the early arterial phase without any leakage of fluorescein in later pictures (Fig. 4). These areas had the appearance of window defects in the pigment epithelium in locations corresponding to the retinal lesions, and looked like those found in retinal photocoagulation burns.[10] No visual field defect could be located despite a careful

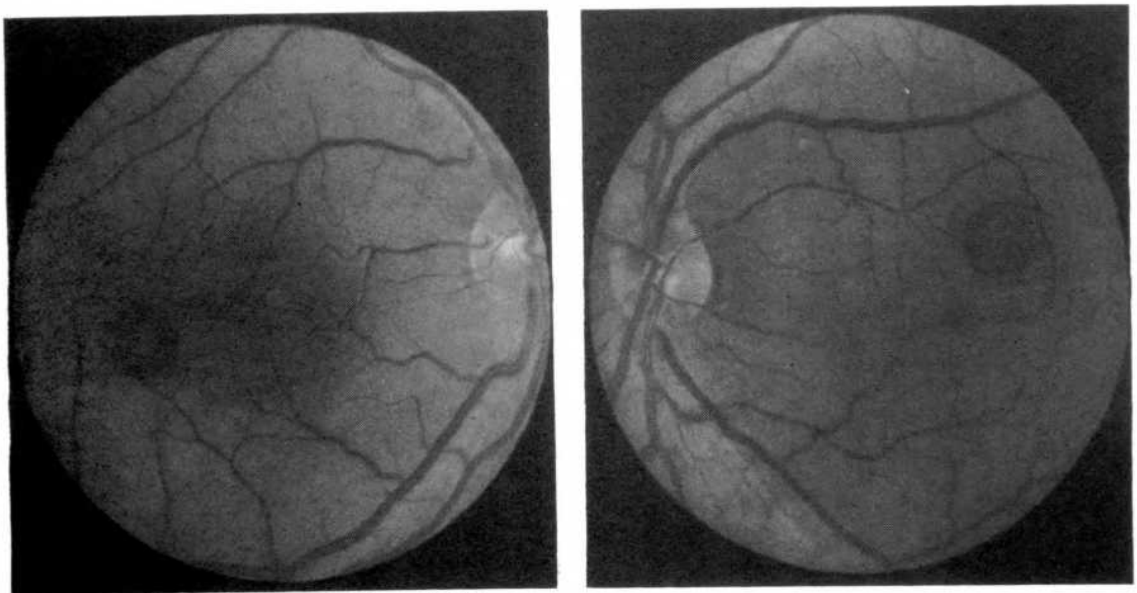

Fig. 3 *Retinal burns in both eyes. L: right eye. R: left eye.*

and detailed search with both tangent screen and computerised Octopus central field analyser (programs 34 and 64).

Discussion

Traditionally, the primary consideration of the ocular hazards of arc welding has been keratoconjunctivitis caused by the ultraviolet radiation, which is produced in large amounts by the welding arc. Ultraviolet radiation is absorbed by the cornea and lens[3] and therefore does not pose a threat to the retina in the phakic eye. However, arc welding emissions cover a wide spectrum, much of which falls within the visible range.[1] The danger of excessive retinal exposure to 'blue light' is well recognised.[4 6 11]

The first case demonstrates a macular burn resulting from prolonged exposure to the radiation of a carbon dioxide MIG welding arc. Although a full recovery was made, the injury was significant, for it shows that a sufficient proportion of the radiation produced by the arc is within the spectral range that can reach the retina to cause retinal injury. The lack of a marked keratoconjunctivitis despite the retinal involvement is of interest and may be explained by spectral analysis of the carbon dioxide arc which produces relatively less radiation in the ultraviolet range than in the visible and near infra-red spectrum (Fig. 5).[12]

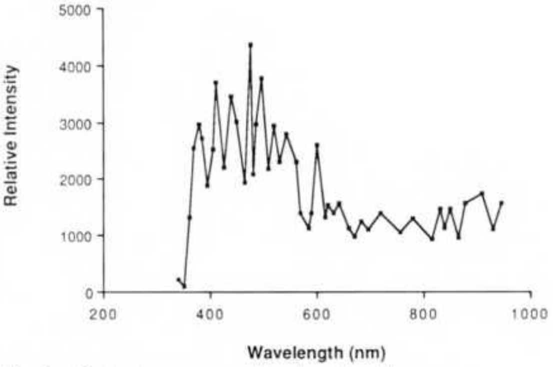

Fig. 5 *Emission spectrum of carbon dioxide arc.*

The macular burns in the second case, which resulted from exposure to radiation from an argon arc, were symmetrically located temporal to the fovea. The principle of physiological diplopia[13] is well illustrated, showing that the welding arc must have been closer to the eyes than the point of visual fixation (Fig. 6). As the intensity of light incident on the retina is inversely proportional to the square of the distance of the source from the eye, this evidence that the patient occasionally had his face very close to the arc is a major factor in this retinal injury.[11 14]

The total amount of radiation from an arc in any given period is approximately proportional to the square of the current and directly related to the arc length (or arc voltage). When using comparable non-professional equipment MIG welders operate at similar voltages but at almost twice the current of rod

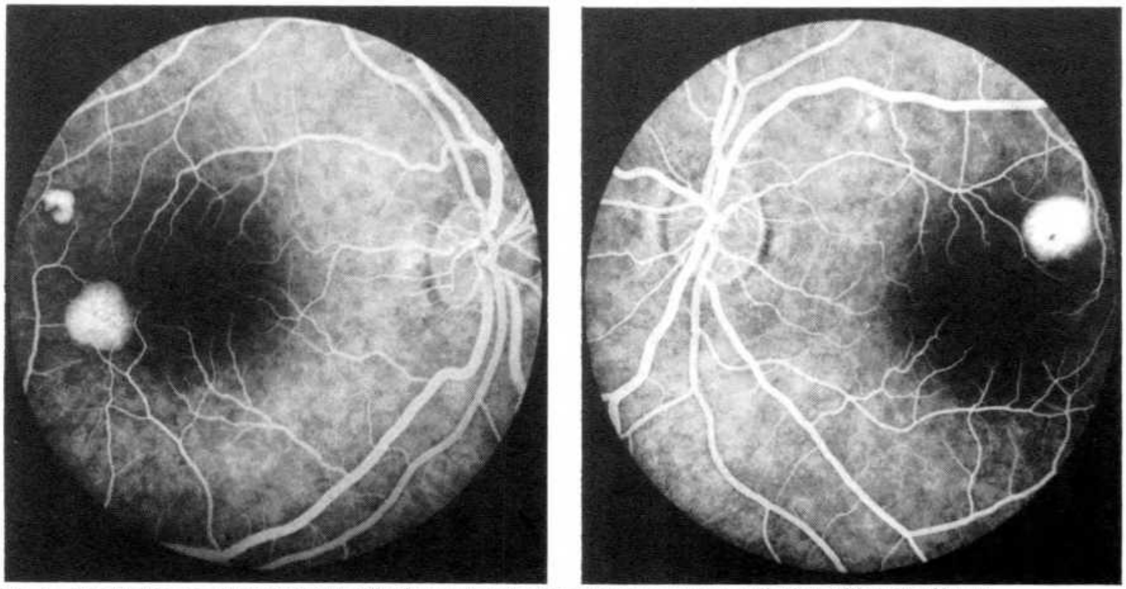

Fig. 4 *Fundus fluorescein angiograms of both eyes showing hyperfluorescent areas at the sites of the retinal burns.*

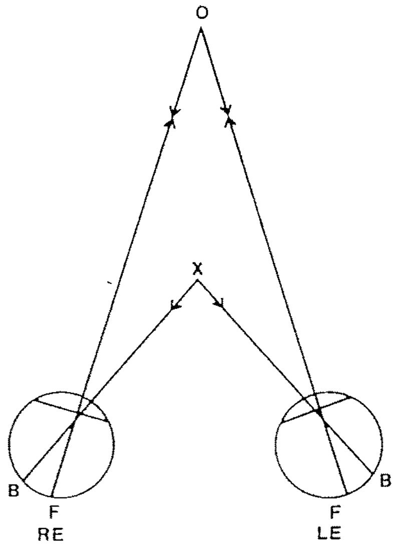

Fig. 6 *Illustration of the principle of physiological diplopia F = fovea, X = welding arc, B = retinal burn, O = fixation object*

arc welders. Whereas a welding rod is of some 2 mm in diameter and produces an arc about 2·5 mm in diameter, the MIG uses a wire 0·6 mm in diameter producing an arc less than 1 mm in diameter. At similar operating currents a MIG produces a current density six times higher (or six times brighter) than a rod arc. MIG welding differs from standard rod arc welding in that the molten metal is protected from oxidation in air by a stream of inert gas rather than by a melted flux. Radiation from a MIG welding arc is not blocked by the surrounding fumes and the molten slag in which a conventional rod arc is submerged. The MIG welding arc is produced by direct current, and its emissions are continuous. A traditional rod arc is driven by an alternating current and so the emissions are pulsed and interrupted, reducing the total exposure for a given period These factors mean that a MIG arc is many times more intense than a conventional arc (Salter GR, personal communication).

The stream of inert gas in a MIG welder allows a controlled, steady arc to be formed. Since every substance has its characteristic ionisation emission spectra, introducing an inert gas to an electric arc will change the spectrum accordingly. When argon is excited by an electrical discharge, the majority of its most intense spectral bands fall within the visible and near infrared range[15] (Fig. 7). The combined emission spectra of argon and carbon dioxide from the gas mix used by MIG welding machines is maximal across the visible spectrum.[12] Such light freely traverses the ocular media (Fig. 8) to be absorbed by the retinal

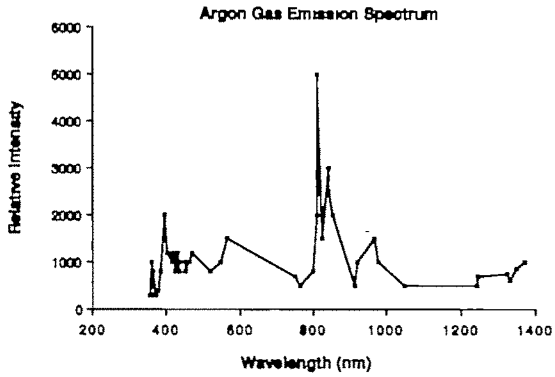

Fig 7 *Argon gas emission spectrum showing the relative intensity of the major emission bands.*

pigment epithelium and choroid[2,8,11] – the basis of argon laser retinal therapy

Time-resolved optical spectra from 200 amp MIG welding arc ignitions have been analysed[14] and show that there is surge of radiation in the ultraviolet and blue light range that occurs within the first 50 milliseconds of the arc being struck. The wave length of the emitted radiation is inversely proportional to the current driving the arc[3] (Salter GR, personal communication) and it is likely that, at the lower currents at which amateur MIG welding machines operate (below 100A), more of the emission will be of a longer wavelength and able to reach the retina during this initial surge on striking the arc.

The filter recommended by the British Standards Protection of Eyes Regulations 1974 for MIG welding is considerably darker than that recommended for rod arc welding, making it more difficult to see through before the arc is struck. The temptation for the inexperienced welder to look round the visor to see

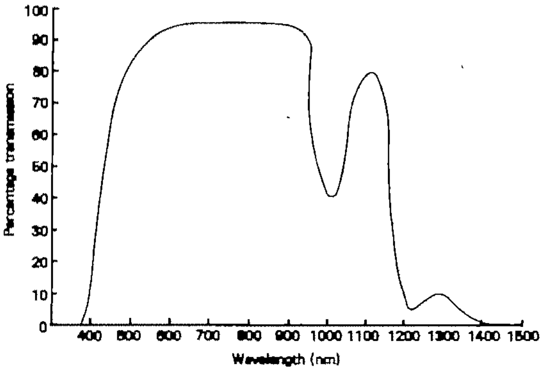

Fig 8 *Percentage emission through ocular media. Spectral transmission curve of ocular media (after Geeraets and Berry[3])*

where the arc will ignite is understandable, especially in poor background lighting conditions where it is impossible to see through the visor. In these conditions pupils would be dilated, allowing a much higher part of the incident light to be focused on the retina. The amount of light falling on the retina is proportional to the square of the pupillary diameter.[13] Pupillary constriction in response to striking the arc is too slow to block the initial 50 ms surge of radiation.

Safety advice given with amateur welding equipment does not adequately stress the risk of not wearing eye protection at all times, the importance of good background lighting, or the danger of welding too close to the eyes.[17]

MIG welding machines were at one time expensive and accessible only to the trained professional. In the past few years they have become readily available at a price within easy reach of the average amateur They can be worked from a standard 13 amp domestic electricity power supply, and, unlike standard arc welding techniques, MIG welding requires very little skill to use and is ideally suited for welding the thin sheet metal on cars.[17]

The intensity and spectrum of radiation of MIG welders differ from those of standard rod arc welders and may present a more serious risk to sight in the unprotected eye than previously recognised, especially in the inexperienced hands of the amateur. It is likely that in future, with the increasing popularity of MIG welding machines, their misuse will give rise to many more cases of macular burns.

I am greatly indebted to Dr George R Salter, of the Welding Institute, Abington, Cambridge, for his help in supplying much of the technical information

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Retinoblastoma in Great Britain 1969–80: incidence, treatment, and survival

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SUMMARY Patients with retinoblastoma diagnosed from 1969 to 1980 have been followed up for periods of up to 17 years. Data from a previous study of patients diagnosed from 1962 to 1968 have been included for analysis of incidence and second primary tumours, and for study of trends in treatment. The registration rate in Britain (which may be about 10% less than the true incidence) is about one in 23 000 live births, approximately 40% of cases being known to be genetic. There is no apparent trend in incidence during the period covered by these two studies. The three-year survival rate is 88%. Patients with bilateral tumours have a better survival rate than those with unilateral tumours for the first few years, but their long-term survival rate is worse because of later deaths from ectopic intracranial retinoblastoma or second primary neoplasms. Older children tend to have a worse prognosis, which is related to the fact that their tumours are diagnosed at a more advanced stage. There is a significantly higher survival rate for boys than for girls; this is partly accounted for by difference in age and stage at diagnosis between the sexes. Children referred to units specialising in the treatment of retinoblastoma have a higher three-year survival rate than those treated at other hospitals. Comparing methods of treatment between the periods 1962–8 and 1969–80, we find there has been a trend towards more conservative treatment. The use of chemotherapy is now usually reserved for recurrences and metastases and for palliative treatment in terminal retinoblastoma.

Retinoblastoma comprises about 3% of all the malignant tumours of childhood. The tumour may occur in only one or in both eyes and may be either unifocal or multifocal in origin. It occurs in both sporadic and inherited forms: the latter, which accounts for about 40% of all the cases, includes all bilateral tumours and a small proportion of unilateral tumours. The observed pattern of inheritance is consistent with that of an autosomal dominant gene.

Kundson[1] suggested that retinoblastoma is caused by mutational events in homologous genes on each of a pair of chromosomes, and that in the hereditary form the first of these mutations is inherited and the retinoblastoma gene is present in every cell in the body. Murphree and Benedict[2] have carried this theory further by postulating that the 'wild-type' allele at the retinoblastoma locus is a suppressor for retinoblastoma; the mutant allele at this locus is recessive at the cellular level, and when there is homozygosity or hemizygosity for this allele retinoblastoma will occur. This would account for the occasional association of retinoblastoma with deletion of part of chromosome 13, where the retinoblastoma gene is missing. Friend *et al.*[3] have identified a segment of chromosome band 13q14, all or part of which is frequently deleted in retinoblastoma and osteosarcoma, and assign to this segment the locus of the 'retinoblastoma gene'.

Material and methods

In this paper we include data about 431 children diagnosed with retinoblastoma in England, Scotland, and Wales between 1969 and 1980. Notifications of the tumours were received from local cancer registries. It is estimated that more than 90% of all retinoblastoma cases occurring in Britain during this period have been ascertained. Medical and epidemiological information has been obtained from the hospitals where the children were treated, and

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from their family doctors. The children have been followed up for at least five years, and for the earlier registrations for up to 17 years, from diagnosis. All surviving children have been flagged at the National Health Service Central Registers at Southport or Edinburgh in order that all subsequent cancers and deaths may be notified to us.

Our previous study of retinoblastoma in Britain[4] included children treated from 1962 to 1968. These children have now been followed up for a further period of 10 years. The total of 699 children with retinoblastoma diagnosed between 1962 and 1980 forms one of the largest well documented series of retinoblastoma available, with probably a better population coverage than any other large series. Some data from the 1962–8 series have been included here in analyses of incidence rates and the occurrence of second primary tumours, and for comparison of treatment regimens during the two periods

Results

INCIDENCE

Incidence rates for retinoblastoma have often been expressed as numbers of cases per million live births and we have followed this convention in the present paper. For the calculation of these rates we have used data for patients diagnosed during 1969–80 from the present paper together with data for 1962–8 from the National Registry of Childhood Tumours maintained by the Childhood Cancer Research Group. All children notified to the national cancer registration system as having retinoblastoma before age 15 will be included in these series. These children will have been born between 1947 and 1980, though for most of these years the coverage of the age range is necessarily incomplete. For instance any child born in 1947 and diagnosed at age 1, or born in 1980 and diagnosed at age 4, will not be included. Allowing for these 'incomplete birth cohorts' we can calculate the incidence of retinoblastoma at each year of age and also the cumulative rate by age 15; these figures are given separately for unilateral and bilateral cases in Table 1. The overall incidence is about 43·9 cases per million births, that is, 1 in 23 000 births. Just over 60% of the cases are unilateral, the incidence rates of unilateral and bilateral cases being respectively 1 in 37 000 and 1 in 60 000 births.

Incidence figures given in other papers range between 1 in 34 000 and 1 in 10 000, but these outer limits are not population based. Vogel[5] suggests that figures of 1 in 28 000 to 1 in 15 000 give reliable limits for incidence. Pendergrass and Davis[6] give the annual incidence in the United States of retinoblastoma in children under 5 (by which age about 95% of cases have occurred) as 11 cases per million, that is, a cumulative rate by age 5 of 55 per million. Our figures are lower than the actual incidence in Britain because we are including only patients registered with retinoblastoma at local cancer registries. It is known that some patients, particularly those who died without treatment, have never been registered, and it is possible that incidence rates quoted here should be increased by as much as 10%.

Of the 699 cases included in the analysis only four were diagnosed more than eight years after birth; the diagnosis of one bilateral case at age 10 years is remarkable. As can be seen from Table 1 the age distributions for unilateral and bilateral cases are quite different. Nearly all bilateral cases are diagnosed in the first three years of life; more than a quarter of unilateral cases are diagnosed after this. Most cases in both groups are diagnosed during the

Table 1 *Incidence of retinoblastoma in Britain, by age at diagnosis*

Age in years	*Incidence per million births*		
	Unilateral	*Bilateral*	*Total*
0	5·0	10·0	14·9
1	7·1	4·6	11·7
2	7·5	1·6	9·2
3	4·0	0·2	4·3
4	1·9	0·1	2·0
5	0·8	0	0·8
6	0·6	0	0·6
7	0·2	0	0·2
8	0·1	0	0·1
9	0	0	0
10	0·1	0·1	0·2
11–14	0	0	0
Cumulative rate by age 15	27·4	16·6	43·9

Table 2 *Incidence of retinoblastoma in children in Britain under the age of 5 years by year of birth*

Year of birth	*Incidence (number of cases per million live births)*		
	Unilateral	*Bilateral*	*All cases*
1962	19	16	35
1963	17	10	27
1964	21	18	40
1965	22	15	36
1966	26	21	48
1967	32	17	50
1968	30	15	45
1969	28	15	43
1970	24	15	39
1971	26	11	38
1972	29	22	51
1973	33	20	53
1974	34	13	46
1975	18	16	34
All years	25	16	42

first five years of life, and for this age group all patients born in the years 1962–75 and notified to a cancer registry are included in this analysis. The overall incidence during the first five years of life per million children born during these years was 25·5 for unilateral cases and 16·1 for bilateral cases These figures are very similar to the cumulative rates for ages 0–4 based on the complete data in Table 1. In Table 2 the incidence rates for the age group 0–4 years are given for single years of birth from 1962 to 1975. It is clear that there is no consistent trend in either the unilateral or bilateral rate.

TYPES OF TUMOUR AND FAMILY HISTORIES

The 431 children in the present study are classified in Table 3 by sex, laterality of the tumours, and whether or not there is a known family history of retinoblastoma. There is histological confirmation of the retinoblastoma for 399 of these patients. The incidence is similar for the two sexes: 221 boys and 210 girls were affected. In 149 (34·6%) children the tumours were bilateral and in 282 (65·4%) children unilateral. Of the unilateral tumours 156 were sited in the right eye and 126 in the left. For one additional child registered during the study period retinoblastoma cells were found only in the suprasellar region of the brain, the eyes and the optic nerves being free of tumour; she has not been included in the analysis. This child had a strong family history of retinoblastoma; her sister and mother were both affected.

Fifty-three children had at least one other relative who had been diagnosed with retinoblastoma. This is 12% of all the children in the study and is in line with other published figures. It is notable that even for the bilateral cases only a minority, 26%, are known to have a family history. Forty children had a parent previously diagnosed with retinoblastoma, and 16 of this group of 40 children had at least one sibling with retinoblastoma Three other children had one sibling with retinoblastoma, and 10 children in the study had only a more distant relative affected with the disease. Of the remaining 378 children with no known family history of retinoblastoma those with bilateral tumours are classified as having the genetic form of the disease One patient with bilateral tumours included in this study, who was first treated at the age of 10 years, has recently had a child diagnosed with retinoblastoma at the age of 2 months.

Table 3 *Numbers of patients with retinoblastoma*

Site	*FH*			*No FH*			*All cases*		
	Male	*Female*	*All*	*Male*	*Female*	*All*	*Male*	*Female*	*All*
Unilateral	7	8	15	135	132	267	142	140	282
Bilateral	18	20	38	61	50	111	79	70	149
All cases	25	28	53	196	182	378	221	210	431

FH=family history

Table 4 *Ages at diagnosis*

Age at diagnosis (months)	*Unilateral*			*Bilateral*			*All cases*		
	FH	*No FH*	*All*	*FH*	*No FH*	*All*	*FH*	*No FH*	*All*
0–5	3	16	19	22	27	49	25	43	68
6–11	1	35	36	9	33	42	10	68	78
12–17	6	20	26	2	18	20	8	38	46
18–23	–	42	42	2	13	15	2	55	57
24–29	1	46	47	2	10	12	3	56	59
30–35	2	29	31	–	7	7	2	36	38
36–41	–	21	21	–	2	2	–	23	23
42–47	–	20	20	–	–	–	–	20	20
48–53	1	16	17	1	–	1	2	16	18
54–59	1	5	6	–	–	–	1	5	6
60–65	–	3	3	–	–	–	–	3	3
66–71	–	5	5	–	–	–	–	5	5
72+	–	9	9	–	1	1	–	10	10
Total	15	267	282	38	111	149	53	378	431

FH=family history.

The study included a pair of monozygotic twins both of whom had retinoblastoma One child was affected unilaterally, and the tumour regressed spontaneously without treatment. His brother, who had bilateral tumours, received radiotherapy to one eye, and the tumour in the other eye also regressed without treatment. One child with unilateral retinoblastoma had an unaffected monozygotic co-twin.

AGES AT DIAGNOSIS

The ages of the children when retinoblastoma was diagnosed ranged from 18 days to 10 years. Table 4 shows the distribution of ages for children with unilateral and bilateral tumours, subdivided according to whether or not there was a family history. These age distributions reflect the incidence rates shown in Table 1. Bilateral cases were diagnosed at an earlier age than unilateral ones; in addition, within each group cases with a family history tended to be diagnosed earlier than those without. The unilateral tumours with no family history had their peak incidence between 24 and 29 months; more than half these children were diagnosed before the age of 30 months. The genetic tumours (bilateral or with a known family history) had their peak incidence in the first six months of life; more than half this group of children were treated before the age of 1 year.

For 130 of the 149 children with bilateral retinoblastoma the interval between diagnosis of the tumours in the two eyes was three months or less. For only six children was this interval longer than a year, and the longest interval was under three years. However, the fact that, when a tumour is discovered in one eye, the other eye is always examined carefully, will probably mean that the second tumour is diagnosed earlier than would otherwise be the case and hence reduce the interval between the two diagnoses.

STAGING

The tumours were staged on the basis of medical records and histology by a modification of the system described by Reece and Ellsworth.[7] Their five-part staging requires more detailed clinical information than that available for most of the cases in this study The stages used and the numbers of unilateral and bilateral cases in each group are given in Table 5. For bilateral cases the staging refers to the eye with the more advanced tumour at diagnosis.

Table 5 *Staging numbers of patients in each category*

Stage	*Numbers of patients*	
	Unilateral	*Bilateral*
I Confined to retina	74	38
II Retinal detachment	60	23
III Optic nerve involved but not beyond cut end	49	24
IV Intraocular spread	66	35
V Optic nerve involved beyond cut end	21	7
VI Extraocular spread	4	3
VII No record	8	19

Table 6 *Treatment of patients with retinoblastoma*

Unilateral

Initial treatment	*No of patients*	*Futher treatment*		
		Enucleation	*RT to socket*	*Conservative**
Enucleation	235 (26)	–	17 (14)	–
Enucleation+R/T socket	30 (10)	–	–	–
Conservative*	15 (2)	4 (1)		4
None (spontaneous regression)	2	–	–	–
Total	282 (38)	4 (1)	17 (14)	4

Bilateral

Initial treatment	*No of patients*	*Further treatment*	
		Enucleation	*Conservative or RT to socket**
Enucleation 2 eyes	9 (1)	–	–
Enucleation 1 eye conservative* treatment other	112 (15)	16 (3)	38 (7)
Conservative* both eyes	27 (3)	5 (1)	13
Nil	1 (1)	–	–
Total	149 (20)	21 (4)	51 (7)

*Conservative treatment includes external radiotherapy to eye, cobalt plaques, light coagulation or cryotherapy

Numbers in brackets are numbers of patients who died from retinoblastoma and ectopic intracranial retinoblastoma

TREATMENT

Table 6 shows the initial and subsequent treatment of 282 children with unilateral tumours and 149 children with bilateral tumours, and the numbers in each category who died. Chemotherapy has not been included in this table but is discussed later.

For the 282 children with unilateral tumours the most usual treatment was enucleation For two children the tumours regressed without treatment; 15 other children received only radiotherapy or light coagulation initially; 13 survived, though four subsequently had the affected eye enucleated. Bilateral tumours were usually treated by enucleation of the more severely affected eye and conservative treatment (cobalt plaques, radiotherapy, light coagulation, or cryotherapy) to the other. Some vision was retained by 108 (84%) of the 129 survivors from bilateral retinoblastoma; for 20 (16%) of these children neither eye had been enucleated

Table 7 compares the treatment given during the periods 1962–8 and 1969–80. There appears to be a trend towards more conservative treatment between the two periods: 5% of children with unilateral tumours in the later period did not have an enucleation as compared with 1% in the earlier period. For the bilateral cases at least one eye was retained for 83% of the children in the later period, as compared with 73% in the earlier.

Chemotherapy was used only in addition to other forms of treatment, never as the sole method. A total of 48 children were treated with cytotoxic drugs. Cyclophosphamide was the drug most generally used. Thirty-nine children were treated with it, in 25 cases in combination with vincristine, methotrexate, or adriamycin. Nine other children were treated with

Table 7 *Comparison of treatment for retinoblastoma between periods 1962–8 and 1969–80*

Years	*Unilateral*		
	Total cases	*Eye enucleated*	*Conservative or no treatment*
1962–8	157	155 (99%)	2 (1%)
1969–80	282	269 (95%)	13 (5%)

	Bilateral			
	Total cases	*Both eyes enucleated*	*One eye enucleated*	*Conservative or no treatment*
1962–8	111	30 (27%)	66 (59%)	15 (14%)
1969–80	149	25 (17%)	101 (68%)	23 (15%)

dexamethasone, triethylmelamine, or vincristine. Table 8 shows the numbers of children given chemotherapy for various reasons and the numbers who died. Thirteen were given drugs as part of the initial planned treatment· 11 received cyclophosphamide, one vincristine, and one triethylmelamine. All 13 survived the retinoblastoma, but two children who had been treated with cyclophosphamide developed osteosarcomas of the leg in their teens. Both children have a strong family history of retinoblastoma.

Six children were given chemotherapy because of the advanced stage of the tumour at enucleation (optic nerve involvement or orbital spread). Four of these children died. The two who survived had been given radiotherapy to the orbit and were treated with a combination of cyclophosphamide, vincristine, methotrexate, and adriamycin for longer than a year Among 29 other children whose tumours were found to be at similarly advanced stages when the eye was enucleated, and who were *not* given chemotherapy there were 12 survivors.

For 29 children the drugs were given because of a local recurrence of the retinoblastoma or distant metastases; all but one of these children died. The child who survived had been treated for six months with cyclophosphamide and vincristine as well as radiotherapy for a recurrence in the orbit and antrum which occurred 18 months after enucleation.*

SURVIVAL RATES AND CAUSES OF DEATHS

Three years after their initial treatment for retinoblastoma 374 of the 431 children were known to be still alive. Two children were lost to follow-up in this period. Of the 55 deaths three were from causes unrelated to retinoblastoma and three from ectopic intracranial retinoblastoma in the pineal gland or suprasellar region. The actuarially calculated three-year survival rate, with deaths from unrelated causes being regarded as losses to follow-up, was 88%. The survival curves for the 282 unilateral and 149 bilateral cases are shown in Fig. 1. The three-year survival rate for the bilateral group (90·5%) was slightly better than that for the unilateral one (86·5%). This is similar to the finding in our previous (1962–8) series.

Table 8 *Use of chemotherapy*

Reason for chemotherapy	*Number of patients*	
	Treated	*Died*
Initial treatment		
Part of initial protocol	13	–
Advanced stage of tumour at enucleation	6	4
Later treatment:		
Orbital recurrence	11	10
Metastatic spread	18	18
Total	48	32

Table 9 *Three-year survival rates for groups of patients subdivided according to various possible prognostic factors*

Factor	*Subgroup*	*Unilateral**		*Bilateral*	
		No of cases	*Three-year survival rate (%)*	*No of cases*	*Three-year survival rate (%)*
	All cases	281	86	149	90
Sex	Male	141	91	79	92
	Female	140	82	70	89
Age (months)	0–5	19	95	49	88
	6–11	36	89	42	98
	12–17	26	96	20	90
	18–23	42	88	15	93
	24–29	47	81	12	75
	30–35	31	77	7	(86)
	36+	80	86	4	(100)
Stage†	I	73	97	38	92
	II	60	90	23	96
	III	49	94	24	96
	IV	66	88	35	94
	V	21	38	7	(71)
	VI	4	(25)	3	(0)
	VII	8	(63)	19	89
Hospital for initial treatment	Major UK referral centre	77	91	94	94
	Specialist eye	74	89	11	91
	With ophthalmic surgeon	126	82	43	86
	Other	4	(100)	1	(0)

*One patient with no follow-up information is excluded
†For definition of stage see 'Methods' section
( ) Fewer than 10 cases

The long-term survival rate, however, was worse for the bilateral cases. The average period of further follow-up for those who survived three years was eight years. No further deaths have been observed among the unilateral cases, but there have been nine in the bilateral group, one from disseminated retinoblastoma five years after the original treatment, five more from ectopic intracranial retinoblastoma, and three from second primary neoplasms

The three-year survival rate for the 1962–8 series of retinoblastomas was 87% The surviving children in that study have now been followed up for between 16 and 22 years. There have been two further deaths from retinoblastoma, and eight children, all with bilateral tumours, have died from second primary neoplasms.

Thus in retinoblastoma most of the deaths occur within three years and are directly attributable to the original disease; very few deaths occur after this. Virtually all of these are in the bilateral group and the great majority are due either to ectopic intracranial retinoblastoma or to second primary neoplasms. The long-term survival rate for the bilateral group becomes worse than that for the unilateral group.

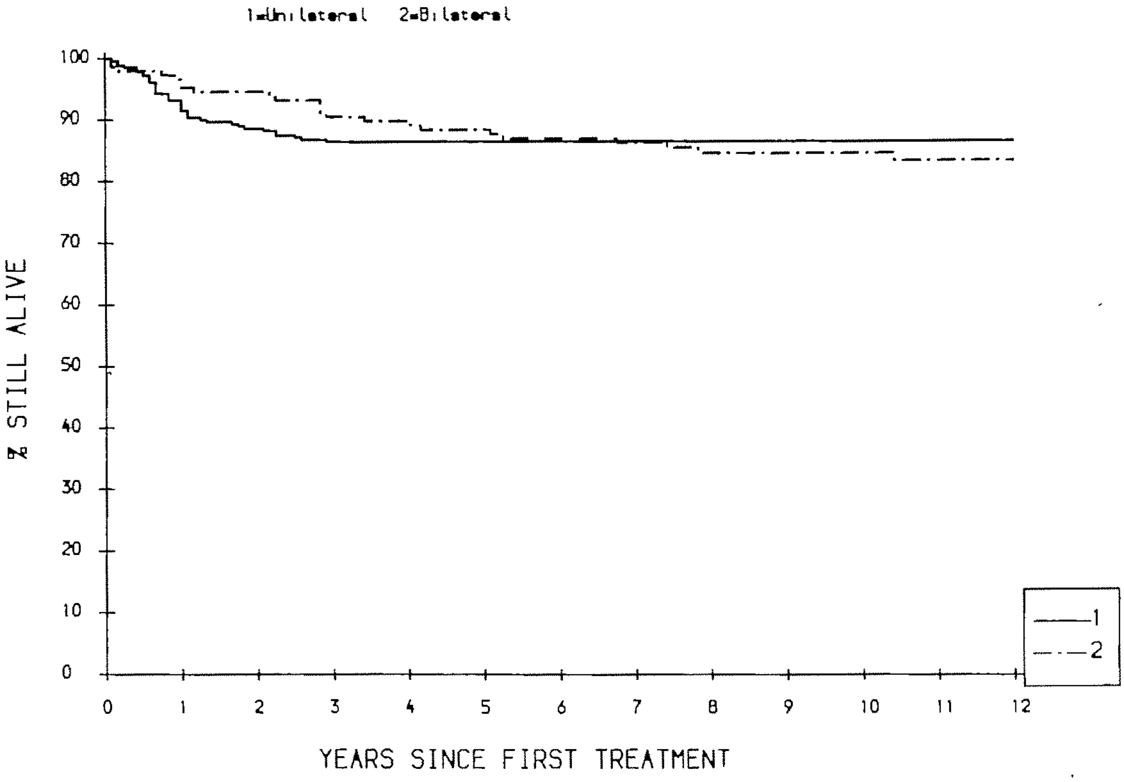

Fig. 1 *Survival for retinoblastoma patients treated 1969–80.*

PROGNOSTIC FACTORS

The effects of various factors on the three-year survival rate are summarised in Table 9.

Tumour stage and age at diagnosis. The staging system used in this paper is described above. As would be expected, there were large and highly significant differences in survival for the different groups (Table 9). It can also be seen from Table 9 that older children, that is, those aged 2 years or more at the time of diagnosis, tended to have a worse prognosis. This is largely accounted for by the fact that these children tended to be diagnosed at a more advanced stage.

Sex. The overall survival rate for males was better than for females in both the unilateral and bilateral groups. The difference is significant ($p<0{\cdot}05$) for the unilateral group and for the two groups combined. This finding is largely attributable to differences in the age and stage distribution for males and females.

Treatment hospitals. Just over a quarter of the unilateral cases and nearly two-thirds of the bilateral cases were given their initial treatment at two London hospitals working jointly as the major United Kingdom referral centre for retinoblastoma. The three-year survival rates for patients treated initially at this centre were 91% and 94% respectively for unilateral and bilateral cases. These were slightly better than those for other specialist eye hospitals (89% and 91%), which in turn were better than those for the remaining hospitals. After allowance is made for the effects of stage and age at diagnosis there is a significant trend ($p=0{\cdot}014$) in survival rate for the unilateral cases; patients treated at the major centre have the best outcome followed by those treated at specialist eye hospitals. A similar analysis for the bilateral cases shows that the difference is not statistically significant. It is possible that this is because the major centre is actually treating the more difficult cases but the staging system used here is not sufficiently sensitive to reveal the effects of such case selection.

SECOND PRIMARY NEOPLASMS

In the present series five children developed second primary neoplasms: four of these were osteosarcomas, three of the leg and one of the orbit, and the fifth child developed acute lymphatic leukaemia. Three of these children have died.

In all, among the 699 children treated for retinoblastoma between 1962 and 1980, and included in our two reports, 609 survived for at least three years. Thirteen of these children have since developed second primary neoplasms of a distinct histology from retinoblastoma, and 11 of the children have died from the second neoplasm Of the total of 13 cases, three osteosarcomas, one brain tumour, and two fibrosarcomas developed within the radiation field. One child treated with high doses of radiation developed leukaemia. These seven second primary neoplasms could have been attributed at least partly to radiotherapy given to the retinoblastoma. However, the other six children all developed osteosarcomas of the leg, outside any field of radiation; indeed one child received no radiotherapy for the earlier retinoblastoma. Nine of 13 children who developed second primary neoplasms had been given cyclophosphamide as part of their treatment. This is a higher proportion than would have been expected from the proportion of patients known to be treatd with cyclophosphamide. However, patients treated with this drug are not representative of the total group of patients, and it is hard to say whether or not it was a factor in the causation of some of the second tumours. A full discussion is given in Draper *et al.*[9]

Discussion

The incidence of retinoblastoma found in the present paper is similar to that from earlier reports. We have found no evidence of a change in incidence in recent years. The age distributions are presented here in more detail than in earlier publications and show the well known difference in age distributions for unilateral and bilateral cases; the latter have a much earlier onset. More than half the genetic tumours were treated under the age of 1 year. On the assumption that two mutational events are necessary for the development of retinoblastoma,[10] this earlier age of onset can be explained by the fact that in genetic cases the first mutation for the retinoblastoma gene is inherited and present in every cell in the body.

Ectopic intracranial retinoblastoma was recognised as a clinical entity only in 1977.[11] During the period covered by the present study eight cases of retinoblastoma followed by ectopic intracranial retinoblastoma were identified, a proportion of 1·9% of all cases, or 5·4% of the bilateral cases. During the earlier period, 1962 to 1968, no cases of trilateral retinoblastoma were recorded, though it may well be the case that some of the children who were said to have died of intracranial or brain metastases actually had pineal retinoblastoma. Among 432 children with bilateral retinoblastoma described by Kingston *et al.*[12] 10 (2·3%) developed ectopic intracranial retinoblastoma.

As compared with our earlier paper there is some indication of a trend towards more conservative treatment. It appears that this has continued in more recent years, at least in United Kingdom centres specialising in the treatment of this disease.

The use of chemotherapy as part of the treatment for retinoblastoma has declined since the 1960s. For the years of treatment 1962 to 1968, 12% of patients were given chemotherapy as part of the initial treatment. This proportion decreased to 4% for the period 1969 to 1980. The two London hospitals which between them treat over 40% of all retinoblastoma patients in Britain have discontinued the use of chemotherapy except for orbital recurrences, metastatic disease, and children with extensive and deep choroidal invasion.

There has been a continuing trend towards centralisation of treatment for bilateral cases. In the period 1962–8 50% of the children with bilateral tumours received their initial treatment at the major UK referral centre; by 1969–80 this proportion had increased to 63%. The proportion of children with unilateral tumours treated at this major centre (27%) was almost identical in the two periods.

There has been very little change in the already high three-year survival rate for retinoblastoma in Britain between the periods 1962–8 and 1969–80, the high survival rate being due to the policy of referral to specialist centres. The great majority of deaths from retinoblastoma occur within three years of diagnosis. Beyond that period, for survivors from genetic retinoblastoma the risk of developing second primary neoplasms assumes an increasing importance in childhood and adult life. The cumulative incidence rate of all second primary neoplasms among survivors from genetic retinoblastoma has been reported as 8·4% after 18 years;[9] for osteosarcoma alone the corresponding figure is 6%. It is now thought[13] that some osteosarcomas may be associated with homozygosity or hemizygosity of the mutant allele at the retinoblastoma locus—13q14 and that the same mutation may predispose towards osteosarcoma.

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N-3-pyridylmethyl-N′-*p*-nitrophenylurea ocular toxicity in man and rabbits

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SUMMARY Ingestion of the rat poison N-3-pyridylmethyl-N′-*p*-nitrophenylurea (PNU) produced ocular toxicity in three humans and in an animal model, the Dutch Belted rabbit. The electroretinogram b wave was especially susceptible to the effects of the rodenticide, and the target tissue appeared to be the retinal pigment epithelium. Injection of PNU itself did not produce ocular toxicity. The poison had to be administered orally. Gentamicin administered orally with PNU prevented the ocular toxicity. Presumably this antibiotic killed those gastrointestinal bacteria responsible for PNU's metabolism into an ocular toxin. L-tryptophan, a known antidote for the lethal effects of PNU, was an antidote for the ocular toxicity when administered orally but not when administered parenterally.

N-3-pyridylmethyl-N′-*p*-nitrophenylurea (Vacor, PNU) is a rat poison that attacks peripheral nerves and the β cells of the pancreas.[1,2] It seems to have a low toxicity for pets and primates. While the LD_{50} for rats was 12 mg/kg, those for dogs and rhesus monkeys were more than 500 mg/kg and 2000 mg/kg respectively. Unfortunately PNU was found to be much more toxic in humans than expected; the LD_{50} for man has been estimated at 5 to 10 mg/kg. The minimum lethal total dose reported in an adult male was between 390 and 780 m.[3] The nucleotide precursors, L-tryptophan and nicotinamide, were found to be effective antidotes in rats;[4] nicotinamide became the recommended treatment of human poisoning.[5]

Diabetes mellitus was a common finding in human survivors. β Cell function tended to return to a variable degree two to three years after ingesting the poision.[6] PNU also produced human peripheral neuropathy and encephalopathy.[7] Orthostatic hypotension tended to be the most persistent and troublesome abnormality, though full recovery has been reported.[8]

In 1981 Mindel and coworkers[9] reported on the ocular findings of a 20-year-old female who had ingested PNU in a suicide attempt 30 months previously. She ultimately developed many of the features of retinitis pigmentosa, namely, atrophic optic nerve heads, attenuated retinal vessels, extinguished electroretinograms (ERGs), and retinal pigment clumping. The role of PNU in producing this constellation of findings was not clear because the patient had received large doses of ergotamine tartrate, up to 6 mg a day for nearly one month, to correct her orthostatic hypotension. Ergotomine tartrate overdosage has been associated with papillitis but not with retinopathy.[10] The present study provides evidence that PNU is toxic to the human eye. In addition an animal model of PNU's ocular toxicity was developed.

Material and methods

HUMAN STUDIES

Three survivors of PNU (Vacor) ingestion were examined. One was female and two were male.

Flash ERGs were recorded under four stimulus conditions: (1) Photopic: cone responses to a 10 μs strong white flash (Grass photostimulator S_8 white)

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against a 438 cd/m^2 background light (normal amplitude >94μV) (2) Flicker: cone responses to a brief exposure of 30 per second strong flashes (normal b wave implicit time <33 ms). (3) Scotopic: an estimate of rod function was obtained using a weak white flash (S_1 white) after 20 minutes of dark adaptation (normal amplitude >194 μV and normal scotopic b wave implicit time <63 ms). (4) Combined rod and cone responses to a strong flash after 20 minutes of dark adaptation (normal amplitude >289 μV). Measurements were made of b wave amplitude (the a wave trough to the b wave peak) and of flicker b wave implicit times (stimulus onset to b wave peak).

RABBIT STUDIES

Adult Dutch Belted (pigmented) rabbits were used exclusively.

Drug administration. N-3-pyridylmethyl-N'-*p*-nitrophenylurea (PNU) was not soluble in water but could be dissolved 300 mg PNU per ml dimethylsulphoxide (DMSO) Multiple doses were each separated by a one-week interval.

An oral dose of PNU, 125 mg/kg body weight, was arbitrarily chosen and was administered by an oral-gastric tube after pentobarbital anaesthesia. Three oral doses were given to each of three rabbits.

PNU was administered by injection to six rabbits. One received intramuscular injections of 125 mg/kg, 250 mg/kg, and 875 mg/kg, that is, a total of 1250 mg/kg. A second rabbit received a single intramuscular injection of 675 mg/kg The third rabbit received two retrobulbar injections, left eye, of 75 mg/kg, that is, a total of 150 mg/kg. Two additional rabbits received single intraperitoneal injections of PNU, 125 mg/kg. The sixth rabbit received an injection of PNU, 20 mg/kg, in the left carotid artery.

L-tryptophan and gentamicin were evaluated as prophylactic agents. L-tryptophan, 0·459 mM/kg, i.e., equimolar to PNU, 125 mg/kg, was administered intravenously 10 minutes before and 1 hour, 3 hours, and 6 hours after an oral dose of PNU, 125 mg/kg to four rabbits. L-tryptophan or gentamicin sulphate was administered orally three times to four rabbits as 1 g suspensions in 10 ml water. Administrations were 4 hours before, 1 hour before, and 4 hours after an oral dose of PNU, 125 mg/kg

Electroretinograms were obtained prior to each PNU administration and at one week intervals after PNU administration. Rabbit pupils were dilated with tropicamide 1% and phenylephrine 2·5% eye drops. The animals were anaesthetised with pentobarbital or xylazine, ketamine was sometimes injected to supplement anaesthesia. Proparacaine hydrochloride 0·5% provided corneal anaesthesia for an 'ERG-JET' corneal contact lens electrode (Nicolet Instrument Corp.). After photopic responses were recorded, the rabbit was dark adapted for 30 minutes and scotopic responses to white and blue light were obtained.

Histological examinations were performed one week after the last administration of PNU. Once the ERGs were recorded the animal was killed with intravenous pentobarbital. The eyes were fixed in glutaraldehyde. One eye of each rabbit was examined by means of light and electron photomicrographs of the retina and pigment epithelium.

Case histories and results

HUMAN STUDIES

Patient 1 was 18 years old when she attempted suicide by ingesting 780 mg of PNU. She acutely developed severe gastrointestinal haemorrhage and an infarct of the right occipital lobe. She survived but became an insulin-requiring diabetic with severe orthostatic hypotension. Eighteen months later she had her first ophthalmic examination. Her visual acuity was 6/6 in both eyes and her retinal vessels and retinal pigmentation were within normal limits. No electrophysiological studies were performed at that time. Subsequently she was put on ergotamine tartrate in increasing doses in an attempt to control her orthostatic hypotension. At a daily dose of 6 mg a day of ergotamine tartrate the patient's symptoms were controlled (blood pressure 130/70 mmHg supine and 120/75 mmHg standing). However, after three weeks of being maintained at this dosage she complained of severe head pain and mildly blurred vision. Ergotamine tartrate was discontinued. Three weeks later, and approximately eight months after her first ophthalmic examination, she was again examined.

Her visual acuity remained 6/6 in each eye, but the arterioles and venules of the retinas were now thread-like. Fluorescein angiography showed decreased vascularity of the optic disc and a tessellated pigmented epithelium. There was no abnormal retinal pigment clumping Electroretinograms were extinguished bilaterally. Retinal thresholds after dark adaptation were markedly elevated in the peripheral retina but only moderately in the posterior pole. The findings on this point were reported in greater detail in 1981.[8] At that time it was assumed that the cause of the retinal changes between the two eye examinations was the ergotamine tartrate. During the next three years she developed a progressive pigment retinopathy (Fig. 1). Mild opacifications and pigment accumulations were seen on the posterior lens capsules (Fig. 2). Her visual acuities were reduced to 6/7·5 bilaterally.

To help clarify the role of PNU in producing this progressive retinopathy, other survivors of Vacor

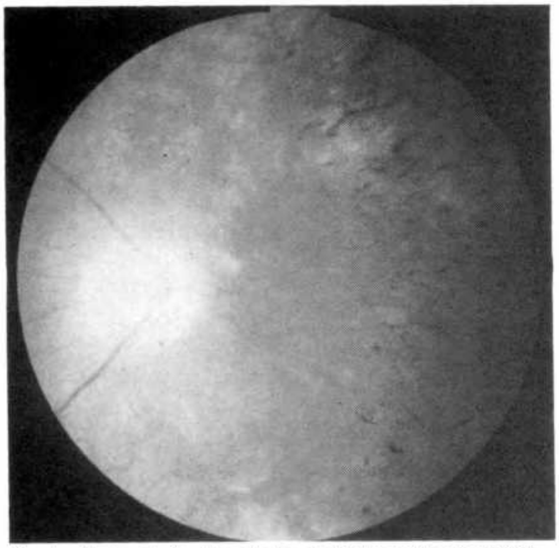

Fig. 1 *Patient 1, fundus photograph 64 months after PNU ingestion. Pigmentary retinopathy is present.*

ingestion were examined. Patient 2 was a 36-year-old white male who had ingested 3·7 g of PNU three years previously. He became an insulin-requiring diabetic. Severe orthostatic hypotension and peripheral neuropathy persisted for 10 months, but then these gradually cleared. He never received ergotamine tartrate. Patient 2 agreed to have electroretinography performed and to have his pupils pharmacologically dilated for this test. But he refused to co-operate for an ophthalmoscopic examination or to have a dark adaptation examination. The electroretinograms were abnormal in both eyes (Fig. 3). The scotopic response to the weak stimulus was subnormal in amplitude and delayed in implicit time (80 to 85 ms). The scotopic response to the strong stimulus consisted only of a decreased amplitude a wave with a longer than normal latency. Under photopic conditions, the amplitude of the b wave to the flicker stimulus was about half the size of the normal recording, with a slight delay in the implicit time (34 ms).

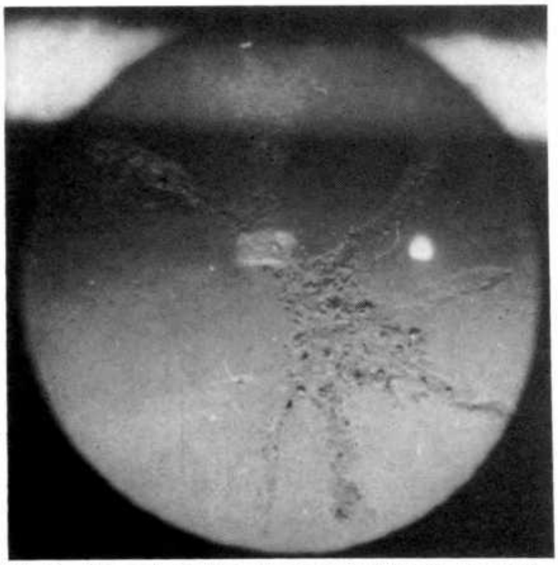

Fig. 2 *Patient 1, slit-lamp photograph of left eye, posterior capsule lens opacification present 64 months after PNU ingestion. The visual acuity was 6/7·5.*

Patient 3 was a 32-year-old white male who had ingested 1·5 g of PNU six years previously. A more complete description of his case history has been reported.[6 11] He was an insulin-requiring diabetic for the first two years after his acute poisoning, but sufficient islet cell function returned thereafter to permit control of the diabetes by diet alone. His toxic peripheral neuropathy, consisting of severe orthostatic hypotension and pain, also resolved after one year. He never received ergotamine tartrate. Patient 3 permitted an ophthalmoscopic examination. Although there was no optic atrophy, narrowing of vessels, or pigment clumping, there were large areas in the peripheral retina with apparent loss of normal pigmentation. The electroretinograms were bilaterally abnormal (Fig. 3). The scotopic b wave response to the weaker stimulus was subnormal in amplitude; the implicit time was difficult to measure. The scotopic b wave response to the brighter stimulus consisted solely of an a wave of normal amplitude. The photopic b waves evoked by a 30 Hz flickering light were within normal limits in amplitude and implicit times.

RABBIT STUDIES

Oral PNU, 125 mg/kg, resulted in loss of the rod portion of the b wave. Administration of two additional doses had little effect on the a wave or on the cone portion of the b wave (Fig. 4). Electron microscopic examination of eyes removed one week after the third oral dose of PNU revealed marked pathology of the retinal pigment epithelium (Figs. 5A–D). There was destructive vacuolisation with loss of phagosomes, nuclei, and cytoplasmic organelles and with a tendency to form large fracture areas. The visual retina was minimally involved. The ganglion cells and inner portions of Müller cells appeared normal. Photoreceptor inner segments had a mild increase in the number of vacuoles, and there was some dropout of photoreceptor outer segments. These photoreceptor abnormalities were considered to be secondary to the almost total destruction of the retinal pigment epithelium (RPE). Behaviourally the

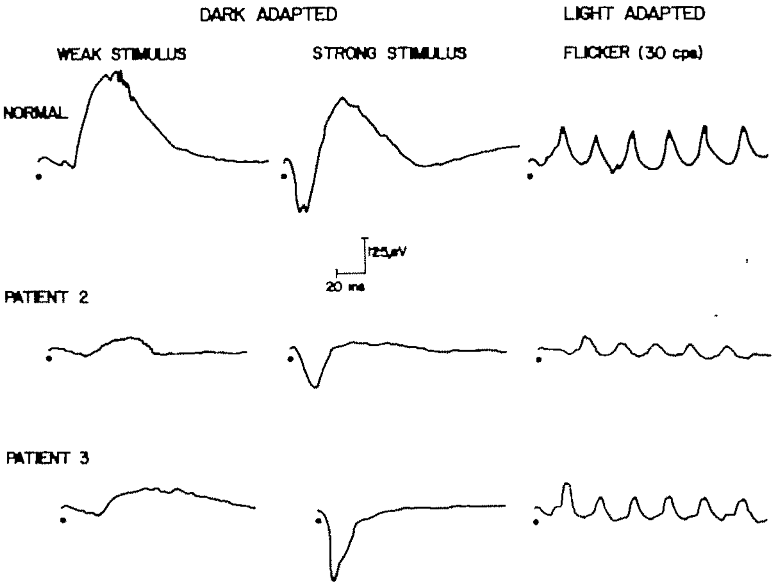

Fig. 3 *Electroretinograms of patient 2 and patient 3 compared with that of a normal 20-year-old female The amplitudes of the scotopic responses of both patients were markedly reduced The scotopic and photopic implicit times of patient 2 were abnormally prolonged Strong=S_8 white, weak=S_1 white*

rabbits did not appear to suffer any visual impairment.

Although oral administration of PNU caused impaired ERG responses and histological evidence of destruction of the RPE, intramuscular, intracarotid artery, retrobulbar, and intraperitoneal injections were without effect. Neither oral nor parenteral PNU produced diabetes mellitus in rabbits.

Multiple intravenous doses of L-tryptophan given within 6 hours of a single oral dose of PNU failed to prevent PNU toxicity. The ERG scotopic responses to blue and white light had been reduced by mean amounts of 64% and 36%, respectively, one week after a single administration of PNU without L-tryptophan. Administration of PNU with intravenous L-tryptophan was associated with corresponding reductions of 58% and 67% Light and electron photomicrographs showed RPE degeneration. However, oral L-tryptophan and gentamicin

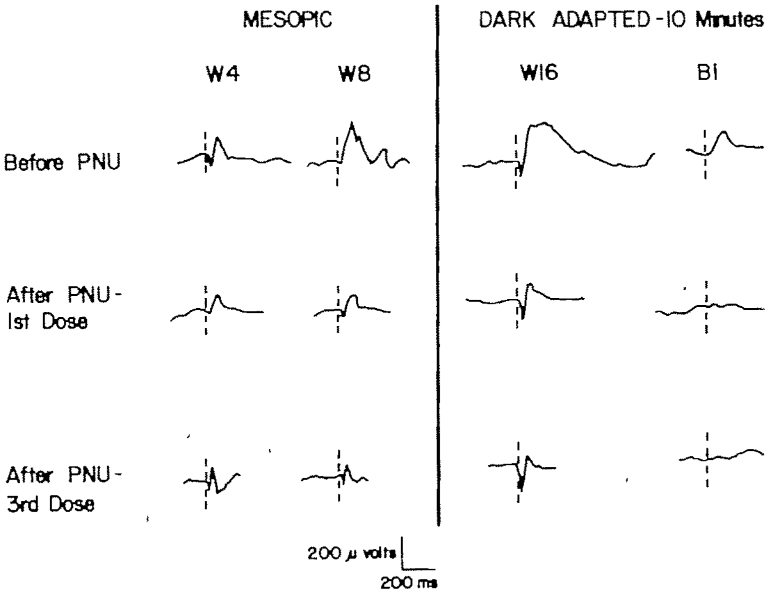

Fig. 4 *Electroretinogram responses of a pigmented rabbit before PNU oral administration and one week after the first and third doses of 125 mg/kg/week. The first dose reduced the rod component After the third dose essentially no rod responses remained The animal was dark adapted for only 10 minutes because of difficulty maintaining prolonged anaesthesia*

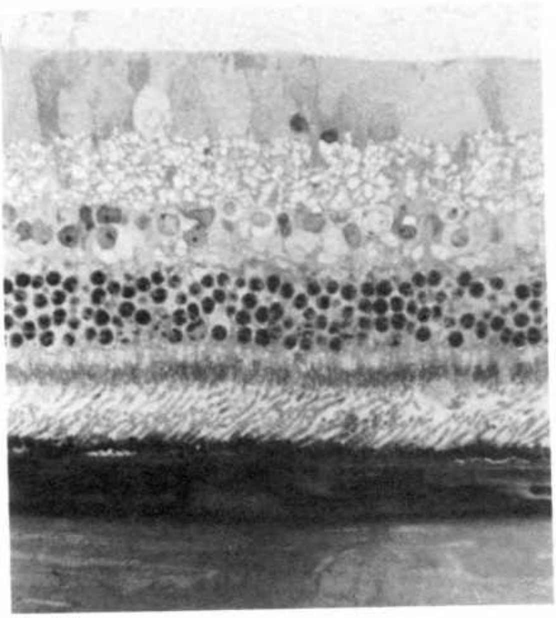

Fig. 5A

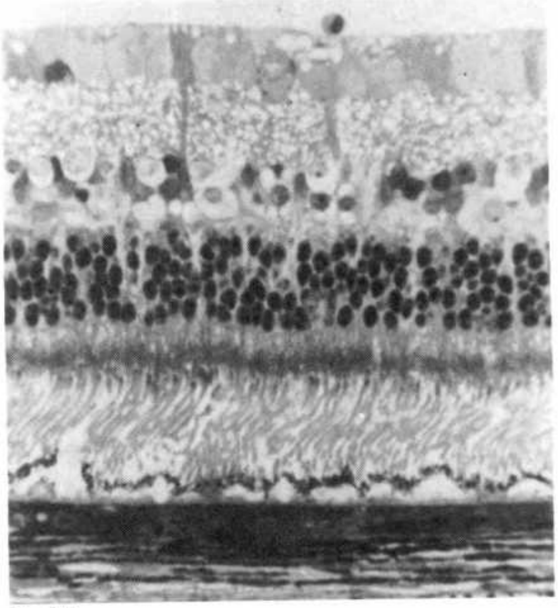

Fig. 5B

Fig. 5 *Photomicrographs of rabbit retinas comparing* (5A, C) *normal tissue with that* (5B, D) *obtained from the rabbit whose ERGs are shown in Fig. 4. The eyes of the latter were removed one week after the third oral dose of PNU, 125 mg/kg. The inner retinas of both appear normal* (5A, B, ×*330*)*. However, the pigment epithelium of the rabbit fed PNU is disrupted. Electron microscopy* (5C, D, ×*2600*) *demonstrates that the pigment epithelum of the PNU-fed rabbit has absence of phagosomes, nuclei, and cytoplasmic organelles and large fracture areas. Bar is 2·9 μm.*

sulphate prevented ERG and histological changes from oral PNU.

Discussion

The initial goal of these studies was to determine whether or not PNU was the probable cause of the progressive pigment retinopathy that developed in patient 1. Among the alternative possibilities were that (1) the large doses of ergotamine tartrate used to

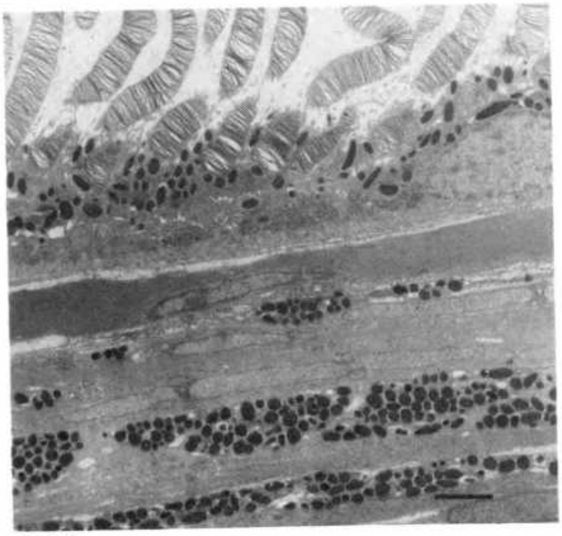

Fig. 5C

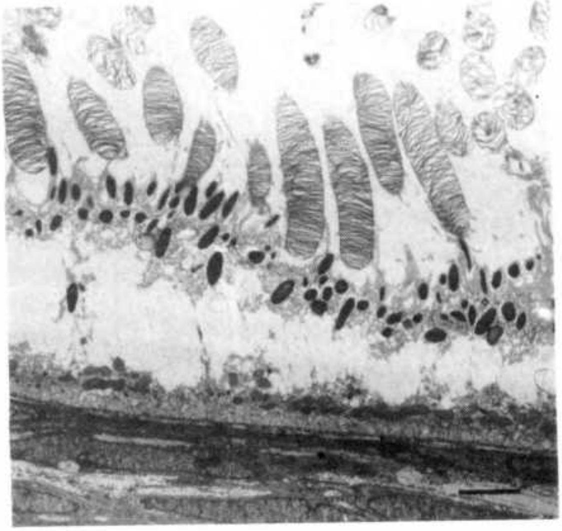

Fig. 5D

treat the orthostatic hypotension had damaged the RPE; (2) PNU and ergotamine tartrate toxicities were additive; and (3) the patient had hereditary retinitis pigmentosa. Similar large doses of ergotamine had been used to treat orthostatic hypotension and had not been associated with ocular toxicity.[12, 13] Ergotamine is less toxic than ergot, and the two reports attributing eye damage to ergotamine ingestion described a papillitis,[11, 14] not pigment retinopathy. Nor has ergotamine tartrate overdosage caused ERG abnormalities.[15] On the other hand many cases of PNU poisoning have occurred without any mention being made of ocular abnormalities. Perhaps the eyes had not been adequately examined.

To investigate this possibility, two other PNU survivors were found who had not been treated with ergotamine. Finding subjects willing to participate was difficult. First, most adult PNU ingestions were suicide attempts, and the survivors were reluctant to be reminded of episodes that now embarrassed them. Secondly, survivors who wanted to commit suicide learned quickly that an overdose of the insulin needed to control their PNU-induced diabetes mellitus was an efficient mode of self destruction. The two survivors consenting to have ERG studies had extinguished scotopic b wave responses and mild changes in their a waves. This selectivity for the b wave was also demonstrated in pigmented rabbits fed small doses of PNU. There seemed to be reasonable evidence to conclude that PNU was an ocular toxin. It should be emphasised that it could not be stated that all, or even most, of patients 1's abnormal electrophysiological responses and anatomical defects were the direct result of PNU ingestion. Ischaemic hypoxia from her gastrointestinal bleeding, and a possible contributing effect from ergotamine, confounded any attempts to assign causality.

Patient 1 had more severe ocular damage, orthostatic hypotension, and diabetes mellitus than the other two patients despite her ingested dose of PNU having been less, that is, 780 mg (patient 1) versus 3·7 gm (patient 2) and 1·5 gm (patient 3) However, patient 1 did not have emesis or develop diarrhoea after ingesting the poison, while the other two did. She waited 48 hours before going to a hospital emergency room. Presumably her absorbed dose of toxin was larger than those of patients 2 and 3.

PNU appeared to alter the human electroretinogram by preferentially extinguishing the b wave, and in patients 1 and 3 seemed to damage the retinal pigment epithelium. An animal model was needed that would demonstrate similar effects. Rodents were not tested, because they were extremely sensitive to the lethal effects of PNU. Rabbits are lagomorphs and phylogenetically closely related to rodents. Dutch Belted rabbits were chosen because their retinal pigment epithelia were pigmented as was man's. Rabbit eyes are relatively large, allowing the ERG electrodes and equipment designed for use on patients to be easily adapted. When Dutch Belted rabbits were fed PNU, they developed both a selective reduction in the ERG b wave and histological evidence of selective damage to the RPE. This damage to the RPE did not result in an ophthalmoscopically identifiable pigment retinopathy, presumably because the experiments were too short, that is, the rabbits were maintained for no more than three weeks after receiving PNU, while patients 1 and 3 developed pigment retinopathy more than four years after ingesting the poison. Behaviourally, the rabbits' vision did not appear impaired. At the dose of PNU used Dutch Belt rabbits also had a fortuitous absence of diabetes mellitus and peripheral neuropathy. Thus they could be easily maintained.

Oral administration of PNU to rabbits had the potential disadvantage of variable drug absorption from the gastrointestinal tract. More uniform blood and tissue levels should result from parenteral administration. However, intramuscular, retrobulbar, intracarotid artery, and intraperitoneal injections of PNU were without effect. As only oral PNU was toxic, it appeared that the drug had to be metabolised in the gastrointestinal tract to become active, presumably by the bacterial flora. Consistent with this theory was the prophylactic effect of oral gentamicin, a Gram-negative bactericidal antibiotic.

L-Tryptophan was also tested as an antidote. Tryptophan is the amino acid precursor of nicotinamide, a proved antidote of PNU's lethal toxicity in rats.[4] Parenteral L-tryptophan did not prevent ocular toxicity from oral PNU. However, oral L-tryptophan did. This suggested that tryptophan was ineffective once the toxic metabolite was absorbed. Oral tryptophan may have competed for the bacterial enzymes that converted PNU or competed for an uptake system responsible for the absorption of the toxic metabolite.

Mildred Schmitterer, MS, of the Department of Ophthalmology, Mount Sinai School of Medicine, New York, prepared tissues for electron microscopy Drs Fred W Deckert, John R Udinsky, Edward Kilbourne, and Gerald M Smith of the Toxicology Department, Rohm and Haas Company, Spring House, Pennsylvania, generously provided PNU and many of its metabolites

This study was supported by the Medical Research Service of the Veterans Administration, NEI Core Center EY-01867, and an unrestricted grant from Research to Prevent Blindness, Inc

This paper is a condensation of a thesis prepared in partial fulfilment of the requirements for membership in the American Ophthalmological Society

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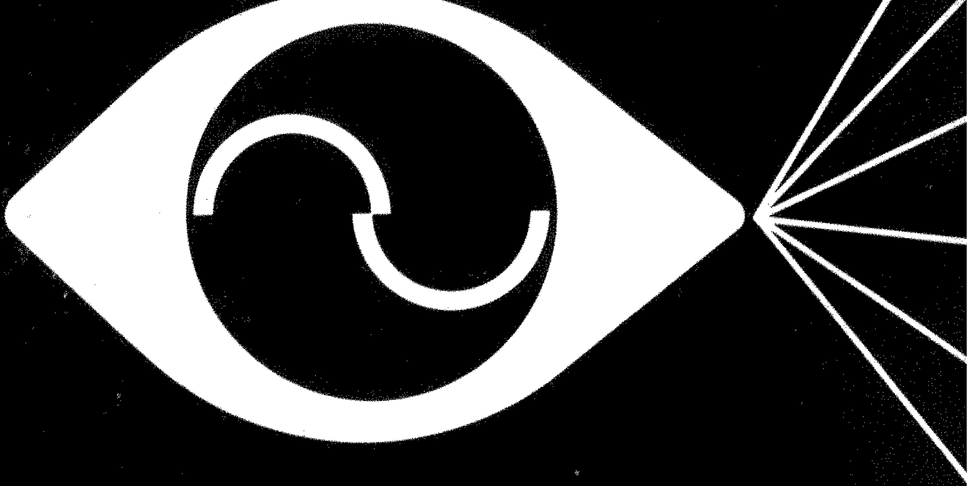

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Teoptic: Abbreviated prescribing information
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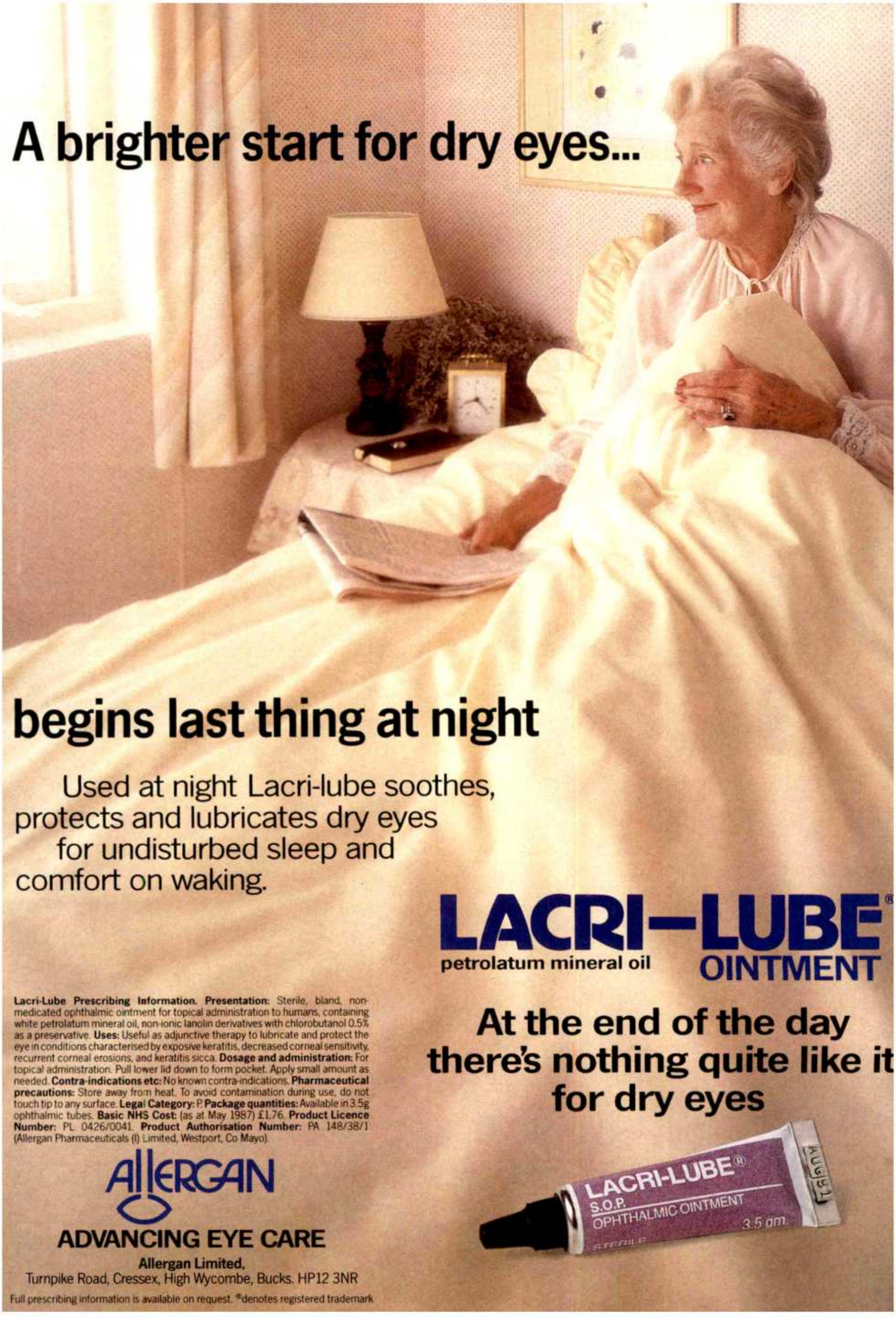

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British Journal of Ophthalmology, 1988, 72, 591–597

Confidence intervals for change in automated visual fields

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SUMMARY Three successive fields of 136 eyes (86 patients) were extracted from our data base containing over 3000 visual fields performed on the Humphrey visual field analyser with program 30-2. Series of fields in which the second field was depressed relative to the first were selected for analysis to determine how much change between the first two fields was required to predict a downward trend as confirmed by the third field in the series. The data were stratified with respect to initial field damage. Seven regions of the visual field were analysed including the upper and lower temporal and nasal quadrants, the superior and inferior Bjerrum regions, and the whole field. Minimally damaged regions required between 4·7 and 5·6 dB change in mean sensitivity, whereas more damaged regions required between 5·5 and 7·2 dB change in mean sensitivity to have 95% confidence that the negative trend would be confirmed by the third field. The superior Bjerrum region was the most sensitive for the detection of change, and the lower temporal region was the least sensitive. We conclude from this series of data that large changes between two successive fields are required to be sure that the changes are due to disease rather than chance fluctuation. Where any doubt exists, the field should be repeated to confirm the reality of change.

Analysing visual field progression is an important part of the management of patients with glaucoma. Unfortunately detecting progression reliably may be difficult. Factors such as short-term (intratest) and long-term (intertest) fluctuation, patient fatigue, patient learning curve, and attention span can cause transient visual field changes which may mimic improvement or deterioration of the overall visual field.[1-4] Over a series of tests these factors should cancel themselves out, that is, errors in the positive direction and errors in the negative direction should be approximately equal, and overall mean sensitivity should stay roughly the same. In practice one must often repeat a visual field test several times before one can determine whether or not an increased depression is due to transient fluctuation or pathological deterioration. However, multiple visual field examinations require considerable expenditure of the patient's time and effort and may unnecessarily delay diagnosis.

In an effort to improve our ability to recognise significant visual field deterioration we analysed a series of three visual fields, to assess the predictive value of the second field in determining the likelihood of a decrease in sensitivity between the first and third field.

Patients and methods

We analysed the field of 136 eyes (86 patients), each of whom had at least three central 30° full threshold fields performed on the Humphrey visual field analyser with program 30-2. The patients were between 21 and 79 years of age (mean 54·7, SD 14·6) All patients had a corrected visual acuity of 6/12 (20/40) or better and pupillary diameter greater than or equal to 3 mm at the time of each test. All patients had glaucoma, with some areas of visual field depression present. The interval between the first and third field was between 4·6 and 30·5 months (mean 16·5, SD 5·4).

For each individual field test the data were analysed by quadrant, superior and inferior Bjerrum area, and for the total field. Fig. 1 displays the regions analysed. The mean sensitivity (MS) in each region

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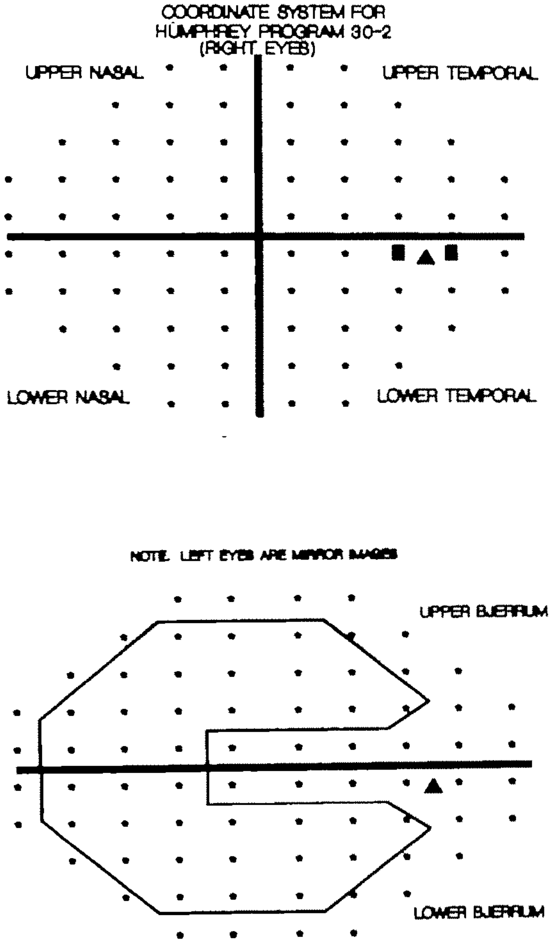

Fig. 1 *Co-ordinate system for the Humphrey visual field analyser program 30-2. Each spot represents a threshold sensitivity measured in dB The two spots marked with a solid box in the lower temporal quadrant were removed from the statistical analysis. The triangle represents the approximate location of the blind spot Points selected for the upper and lower Bjerrum regions are shown in the lower part of the figure.*

was determined by adding the individual threshold values in dB and dividing by the number of values. The two points closest to the blindspot in the lower temporal region were eliminated from the analysis.

Each series of fields was coded for each region as to possible relationships between fields 1, 2, and 3. Fig. 2 shows the possible arrangements of field scores. For the analysis we considered only series where a respective region of the second field was depressed relative to the first field. After this selection 79 eyes were available for analysis.

Regression models were constructed to determine what regional change between the first and second field was required to predict that the third field would show a depression relative to the first field. Depression of the third field was defined as the MS of field 3 being 1 dB below that of field 1. Each region must have had a drop in total sensitivity of 1 dB times the number of spots in that region. This represented a 19 dB total drop for the quadrant regions or a 74 dB drop for the entire field.

The data were stratified in accordance with degree of field damage at the first field. Each region with an MS of greater than 25 dB was placed in one group labelled 'minimal field damage', and regions with an MS of less than or equal to 25 dB were placed in another group labelled 'moderate field damage'.

Results

Table 1 displays the mean sensitivities and standard deviations for each of the regions where the second field was depressed relative to the first.

Tables 2 and 3 report the results for the regression models studied to determine the amount of change required between the first and second fields to predict

Table 1 *Summary of three fields for each region*

Quadrant	*First*		*Second*		*Third*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
UN	21·1	4·1	18·7	4·5	19·2	4·8
UT	22·3	5·2	19·8	5·9	20·7	5·7
LN	24·2	4·0	21·8	4·9	22·2	4·9
LT*	26·0	3·2	23·9	4·1	24·6	4·0
Total	22·6	4·9	20·6	5·4	20·9	5·4
SB	21·4	3·9	19·1	3·8	19·6	4·2
IB	24·5	3·6	22·5	4·0	23·1	4·2

*With blind spot points removed UN=upper nasal UT=upper temporal LN=lower nasal LT=lower temporal SB=superior Bjerrum IB=inferior Bjerrum

Table 2 *Model Drop MS field 1 to 2 versus change MS field 1 to 3. Minimally damaged fields*

Region	*R^2*	*Slope*	*Intercept*	*p*
UN	0·05	0·17	1·88	0·1772
UT	0·22	0·27	1·60	0·0056
LN	0·14	0·22	1·66	0·0145
LT	0·05	0·12	1·75	0·1196
Total	0·05	0·08	1·71	0·1941
SB	0·07	0·19	1·98	0·1172
IB	0·16	0·29	1·37	0·0035

For abbreviations see Table 1

Regression coefficients as predicted from each model R^2=R^2 value. Slope=slope of best fit line through points Intercept=intercept of best fit line on the axis corresponding to the dependent variable P=Probability that the slope is not equal to 0

Table 3 *Model. Drop MS field 1 to 2 versus change MS field 1 to 3. Moderately damaged fields*

Region	R^2	*Slope*	*Intercept*	*p*
UN	0·30	0·34	1·85	0·0001
UT	0·22	0·33	2·40	0·0028
LN	0·23	0·30	2·43	0·0106
LT	0·05	0·10	2·32	0·3539
Total	0·12	0·22	1·86	0·0276
SB	0·30	0·35	1·67	0·0006
IB	0·16	0·21	2·09	0·0335

For abbreviations see Table 1. See footnote to Table 2

Table 4 *Required change field 1 to 2 in dB*

Region	*Degree of damage*	
	Minimal	*Moderate*
Upper nasal	*	6·50
Upper temporal	4·74	6·91
Lower nasal	5·22	7·20
Lower temporal	*	*
Total field	*	5·49
Superior Bjerrum	*	5·76
Inferior Bjerrum	7·85	5·55

*No significant regression model found for these regions

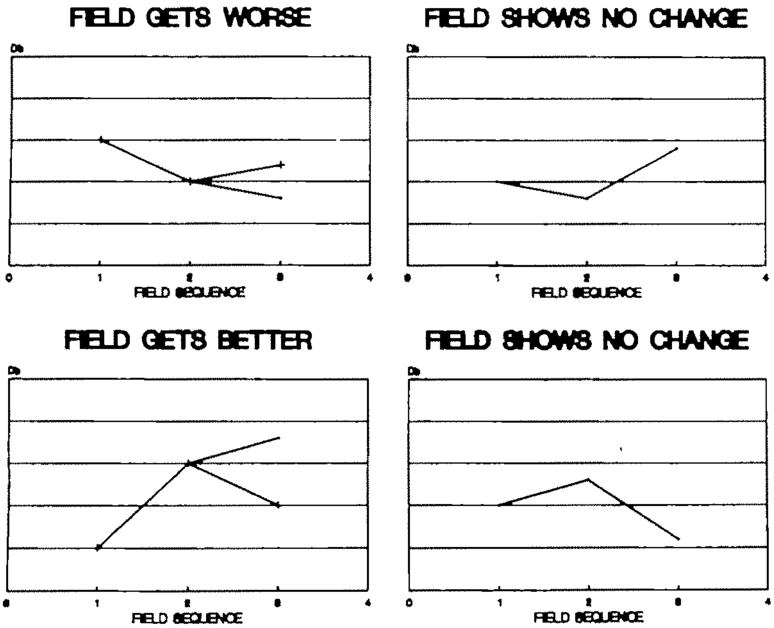

Fig 2 *Possible patterns of response for each patient's series of three consecutive fields A series was considered worse if the third field was at least 1 dB below the first field, or the slope of the best fit line through the three fields was negative.*

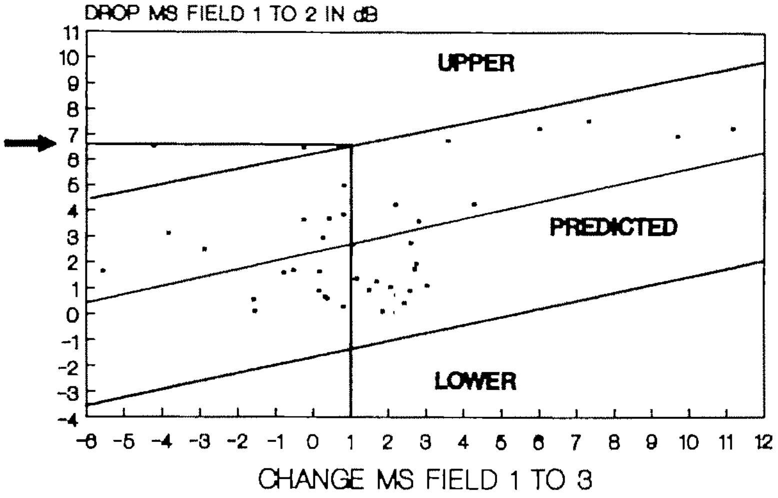

Fig. 3 *Graphical representation of the method used to determine the 95% confidence level for the amount of change required between the first two fields which would predict that the third field would confirm a downward trend in the series*

a downward trend in the series as confirmed by the third field. The regression equations were solved for the dependent variable (drop required between fields 1 and 2) by means of the change in MS between field 1 and field 3 as the independent variable. This value plus the product of the standard error of the model and the *t* statistic, adjusted for degrees of freedom and desired confidence interval, yields the upper confidence level for the point where the patient's field is confirmed as getting worse.

Fig. 3 graphically displays the 95% confidence level for change from field 1 to field 2 required to predict that field 3 will be depressed by at least 1 dB relative to field 1 in the upper temporal region of moderately damaged fields. Table 4 reports the amount of change in MS required between fields 1 and 2 to predict with 95% confidence that field 3 will be below field 1 by at least 1 dB for each of the regions studied for both minimally and moderately damaged fields.

Figs. 4 and 5 demonstrate plots of required change from fields 1 to 2 versus varying confidence intervals for confirmatory change in field 3 in minimally and moderately damaged fields.

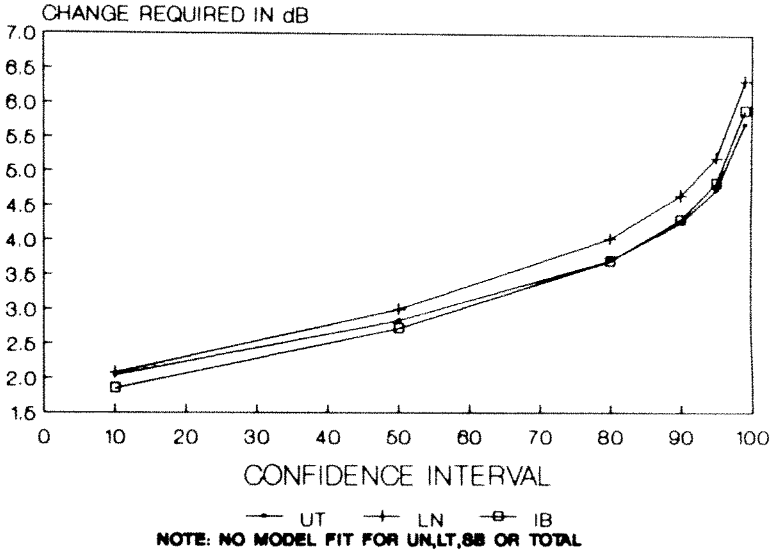

Fig. 4

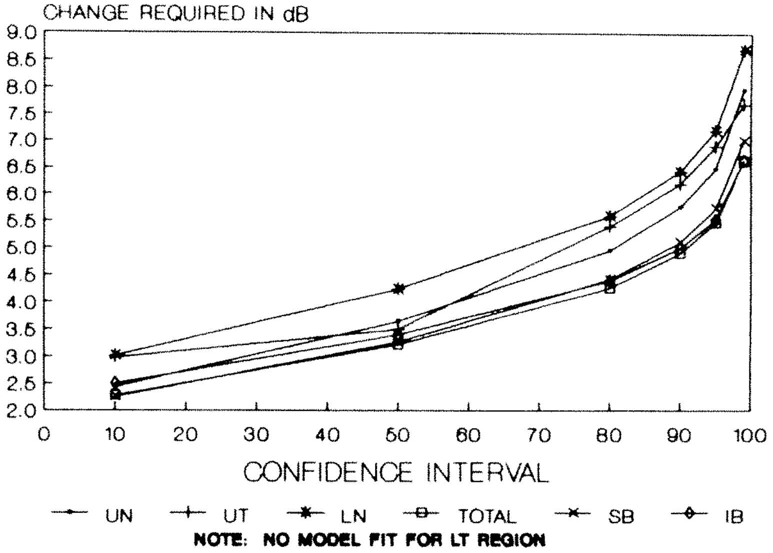

Fig. 5

Figs. 4 and 5 *Plots of drop in MS required to predict a downward trend in the series as confirmed by the third field versus confidence intervals for this confirmation. Fig. 4 shows required change in minimally damaged fields. Fig. 5 shows required change for moderate to severely damaged fields.*

Discussion

The visual field examination is but one of a series of tests and evaluations that ophthalmologists use to determine whether or not a patient's glaucoma is progressing. Our data indicate that, for eyes with visual acuity better than or equal to 20/40 and pupil size greater than or equal to 3 mm, a decrease in mean sensitivity of between 4 and 7 dB (depending on the region analysed) is required to predict with great reliability a continuing downward trend in sensitivity. The converse is also true: as the change from field 1 to 2 becomes smaller, the probability of a continuing downward trend is less. An average loss of 3·2 dB in moderately to severely damaged fields corresponds to the 50% confidence interval. In other words, when the average loss per point in a given region between the first two fields in our series is 3·2 dB, 50% of the time the third field will confirm the downward trend.

It should be noted that no statistically significant regression model could be constructed for the lower temporal region, even when the two points closest to the blind spot were removed from the analysis. This is due to the fact that there was very little deterioration between the successive fields in this region.

What is perhaps most striking about our findings is that the degree of depression between the first and second fields must be quite extensive before the confidence level is high enough for the third field to confirm depression. If on the Humphrey field analyser a normal field might have an MS of 30 dB in a given quadrant, then approximately 20% (6 dB) loss of this sensitivity must occur to have a high predictive value.

Large regions, namely, the entire field, require less change per spot, but more total loss, than smaller regions or individual points. In the analysis using moderately damaged fields the upper temporal quadrant required a 6·9 dB change per point, whereas the total field required only a 5·49 dB change per point to be 95% sure that a third field would confirm this downward trend.

Less total change is required by region than by total field. From the above example the upper temporal quadrant requires a total change of 6·9×19 points, or 131 dB, whereas the total field would require 5·49×74 points (excluding the two points nearest the blind spot), or 406 dB. Therefore analysing individual regions for change is more sensitive than looking at the entire field.

More importantly, regional analysis may detect change that is not evident from full field analysis, as demonstrated by the fields in Fig. 6. In this series the drop in total mean sensitivity between fields 1 and 2 is 3·5 dB. Field 3 is depressed relative to field 1 by 3·1 dB indicating the 40–50% confidence level. However, the lower Bjerrum region is depressed by 7·8 dB, which represents the 99% confidence interval from our models. Field 3 confirms the change for this region.

Change in mean sensitivity, even though large, may be due to fluctuation rather than pathological change. Figs. 7 and 8 demonstrate grey scales of two series of visual fields where the second field is depressed relative to the first by 3·95 dB (70% confidence) and 5·25 dB (92% confidence) respectively. The third field in both these series failed to confirm this downward trend.

Regional analysis can confirm field deterioration suspected from looking at the entire field. Fig. 9 shows a series of fields where the MS of the second field is depressed relative to the first by 5·22 dB (92% confidence). In this series the lower temporal quadrant is depressed by 6·74 dB in the second field, corresponding to the 99% confidence interval. This region confirms the loss suspected in the total field analysis at a very high confidence level.

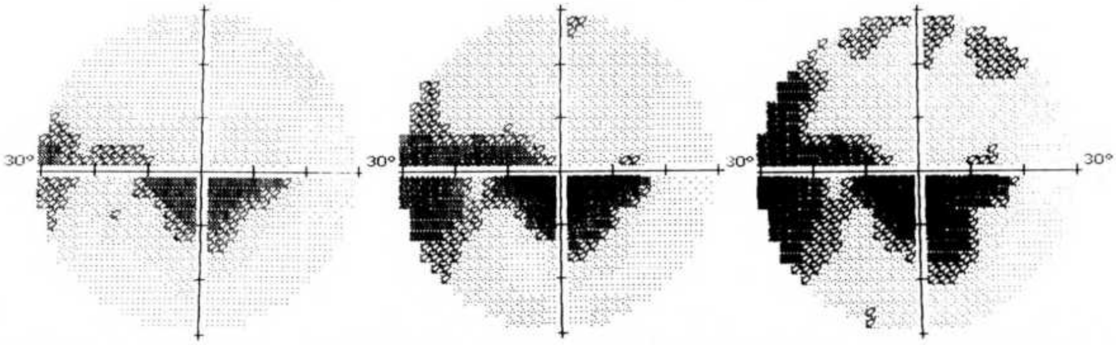

Fig. 6 *Grey scales of three sequential visual fields performed on a 58-year-old male with glaucoma. There is a 3·5 dB change in total mean sensitivity between fields 1 and 2. The lower Bjerrum region shows a change in mean sensitivity of 7·8 dB which corresponds to the 97% confidence interval and is confirmed by the third field.*

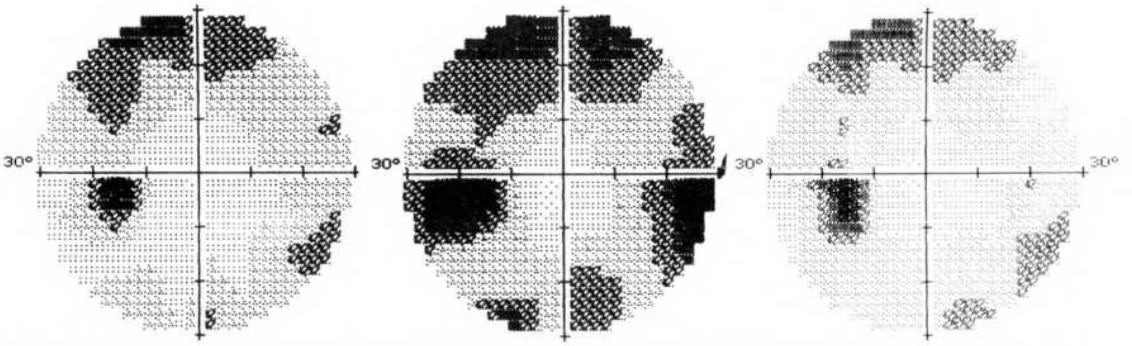

Fig. 7 *Grey scales of three sequential visual fields performed on a patient with primary open angle glaucoma. The mean sensitivity of the second field is depressed 3·95 dB relative to the first. The third field, performed four months later, has returned to nearly the same mean sensitivity as the first.*

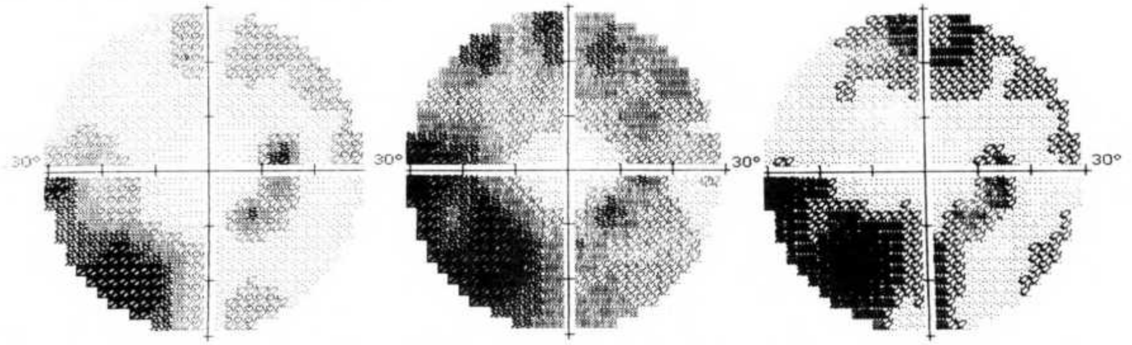

Fig. 8 *Grey scales of three sequential visual fields performed on a 61-year-old patient with primary open angle glaucoma. The second field is depressed 5·25 dB relative to the first, but the third field has returned to a mean sensitivity 0·82 dB greater than the first.*

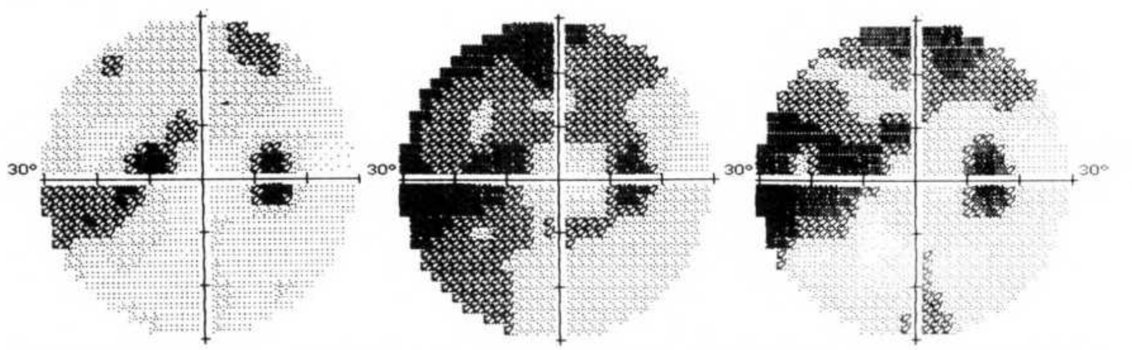

Fig. 9 *Grey scales of three sequential visual fields performed on a 76-year-old male with glaucoma. The 5·22 dB drop in mean sensitivity was confirmed with a third field. The upper and lower temporal quadrants changed in mean sensitivity by 6·26 and 6·74 dB respectively, corresponding to 95% confidence intervals as predicted by our models for moderately damaged fields.*

Werner *et al.*[5] presented data suggesting that long-term fluctuation at any single point could exceed 35%. Thus a moderately damaged point corresponding to 23 dB could fluctuate 8 or more dB between subsequent tests. It was also shown that fluctuation increases with eccentricity and with amount of damage.[6 7] Our data confirm these findings. We also recognised that greater change is required to reach the 95% confidence level in more severely damaged visual fields (Table 4).

Greater numbers of field examinations will lend themselves to more precise statistical analysis. However, time, cost, and the patient's endurance limit the numbers of fields that can reasonably be performed. We have examined the methodology followed by many practitioners, that is, the sequential comparison of routinely collected visual fields. We are not advocating this as the best use of computerised perimetry, but rather are indicating the magnitude of change required if the practitioner wishes to use this technique.

Arguments can be made that two or three baseline fields performed within a short period of time would provide a better starting point for recognition of change. This may be so but remains to be proved. Until then practitioners need to recognise the potential fluctuation in visual fields over time.

In practice one analyses multiple factors when making therapeutic decisions about glaucoma patients. The most prominent of these factors include the patient's intraocular pressure, the cup to disc ratio, the presence or absence of optic disc haemorrhage, and visual field deterioration. Unfortunately, data on the predictive validity of these factors are incomplete.

If doubt exists about the results of a particular field test, it is wise to repeat the test reasonably soon to obtain confirmation.

The visual field examination measures a biological function, and fluctuation is to be expected in the results. It is our goal to create an awareness of the magnitude of this fluctuation as it occurs in an actual clinical setting.

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Dopamine-2 receptor blockade does not affect the ocular hypotensive action of timolol

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SUMMARY We have shown that metoclopramide, a dopamine-2 antagonist, failed to antagonise the ocular hypotensive action of timolol. The practical implication of combining dopamine agonists with β-adrenoceptor antagonists in the treatment of glaucoma is discussed.

Mechanisms other than β-adrenoceptor antagonism were suggested by some workers involved in the mechanism of hypotensive action of timolol in the eye The D-isomer of timolol (D-timolol) was shown to have potent ocular hypotensive action in animals associated with minimal classical β-adrenoceptor antagonistic action.[1 2] Watanabe and Chiou[3] showed that incubation of the rabbit iris root ciliary body preparation with timolol resulted in a decrease in dopamine content when compared with control preparations. Alcondon *et al.*[4] showed that pretreatment of rabbit eyes with atropine significantly antagonised the ocular hypotensive action of timolol and propranolol.

Mekki *et al.*[5-7] showed that stimulation of dopamine-2 receptors can reduce intraocular pressure (IOP) in man. Mekki and Turner[7] and Lavin and Andrews[8] have also shown that the two dopamine receptor blockers, metoclopramide and haloperidol, have no ocular hypotensive action in man, though metoclopramide antagonises the ocular hypotensive action of bromocriptine.[7]

We have investigated whether stimulation of dopamine-2 receptors is involved in the mechanism of the ocular hypotensive action of timolol by observing the effect of blocking these receptors with metoclopromide prior to the administration of timolol.

Subjects and methods

Six healthy volunteers, three males and three females, aged 22–35 years participated in this study. None had a history of asthma or wore contact lenses. Each volunteer attended on three occasions one week apart at the same time of day. In each session baseline measurements of intraocular pressure (IOP) were taken by non-contact tonometry[9] and followed by one of three treatments: placebo, timolol alone, or metoclopramide followed by timolol Three IOP measurements were taken at each time point and the mean was recorded. The treatment administration was arranged as follows: an intravenous injection of either metoclopramide 10 mg or matching placebo was given, folowed 15 minutes later by one drop of timolol 0·5% or placebo into the conjunctival sac of the left eye only, resulting in the three combinations. The treatments were given double-blind balanced design based on two Latin squares. IOP was then measured at one and at two hours after instillation of timolol eye drops. The study has been approved by the local Ethics Committee.

The baseline readings were compared by 2-way analysis of variance, and within-subject comparison revealed no statistical difference between the three trial sessions. The areas under the post-treatment response versus time curves for each subject on each treatment were calculated and compared by analysis of variance. The areas under the curves are presented in Table 1.

Results

A graphical representation of the IOP responses is shown in Fig. 1. Timolol resulted in a significant fall of IOP when compared with placebo on both occasions, that is, alone ($p<0·05$) and after metoclopramide ($p<0·01$). There was also a small decrease of IOP in the right (untreated) eye, but this did not reach statistical significance.

Correspondence to Professor P Turner.

Table 1 *Areas under the post-treatment intraocular pressure response versus time curves*

Subject	*Placebo*	*Timolol*	*Metoclopramide and timolol*
Left eye			
1	8·5	6·7	6·3
2	5·9	3·9	3·5
3	9·9	9·5	9·5
4	10·9	7·2	5·5
5	9·7	9·7	9·5
6	8·0	7·7	6·4
Right (untreated) eye			
1	8·3	7·4	8·7
2	8·9	5·7	5·7
3	15·7	12·5	15·5
4	10·5	8·7	8·2
5	11·5	9·7	12·2
6	9·2	9·5	8·4

There was no difference between the two responses to timolol: F(1,10)=0·09, p>0·35.

Discussion

We have investigated the effect of pretreatment with metoclopramide on the ocular hypotensive action of timolol. As the aim of this experiment was not to confirm the absence of an ocular hypotensive action of metoclopramide[7] or to study other interactions, we did not include an additional treatment with metoclopramide alone.

These results show that pretreatment with metoclopramide, a selective dopamine-2 receptor antagonist, did not affect the ocular hypotensive action of timolol. We therefore conclude that stimulation of dopamine-2 receptors does not have an important role in the mechanism of action of timolol in lowering IOP. In high concentrations metoclopramide can also block dopamine-1 receptors,[8] but even if this occurred in our study it did not affect the ocular hypotensive action of timolol. The dose of metoclopramide used was the same as that which blocked the action of bromocriptine in our earlier study.[7]

Although results from animal experiments show that dopaminergic blockade can be associated with an ocular hypotensive action,[11,12] and that the action of timolol may be related to the dopaminergic system,[3] it seems that this is unlikely in man

Bromocriptine and timolol, therefore, lower IOP by different mechanisms. This finding is not merely of academic interest. One or more dopamine agonists may be introduced for the treatment of glaucoma. If so, a combination with a β-adrenoceptor antagonist may result in potentiation of the ocular hypotensive action.

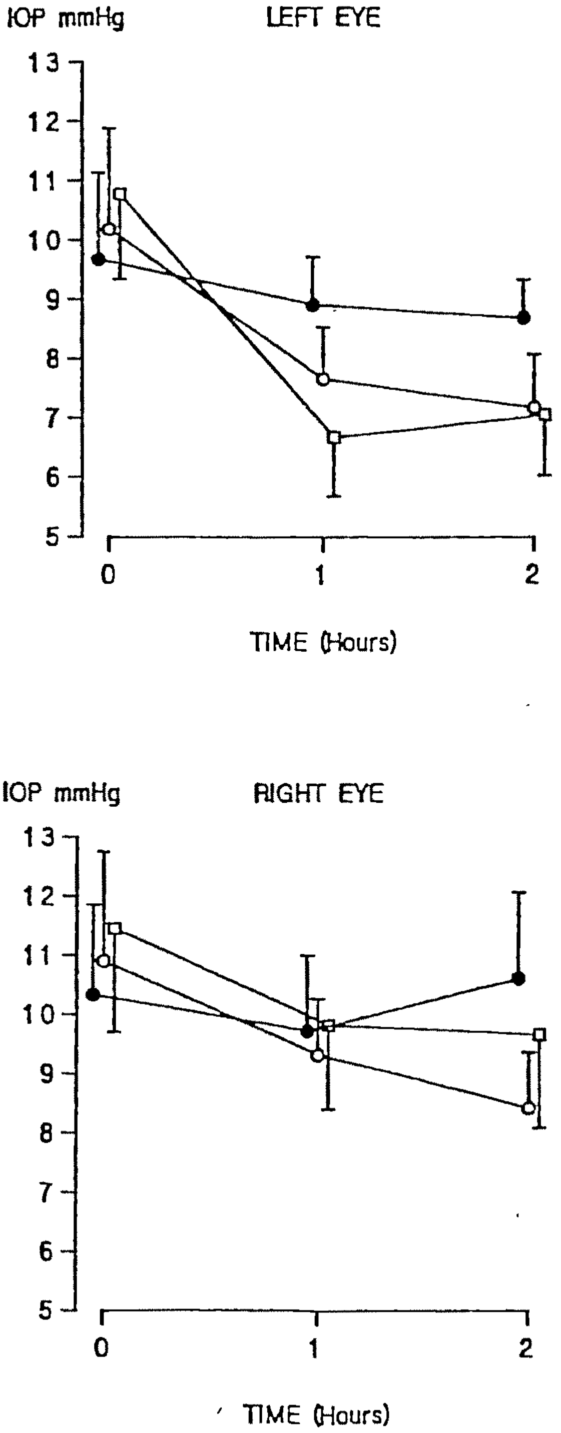

Fig. 1 *IOP changes (mean±SEM) after (□) metoclopramide and timolol, (○) timolol alone, and (●) placebo.*

We thank Dr M A Rhandawa for assistance in the study

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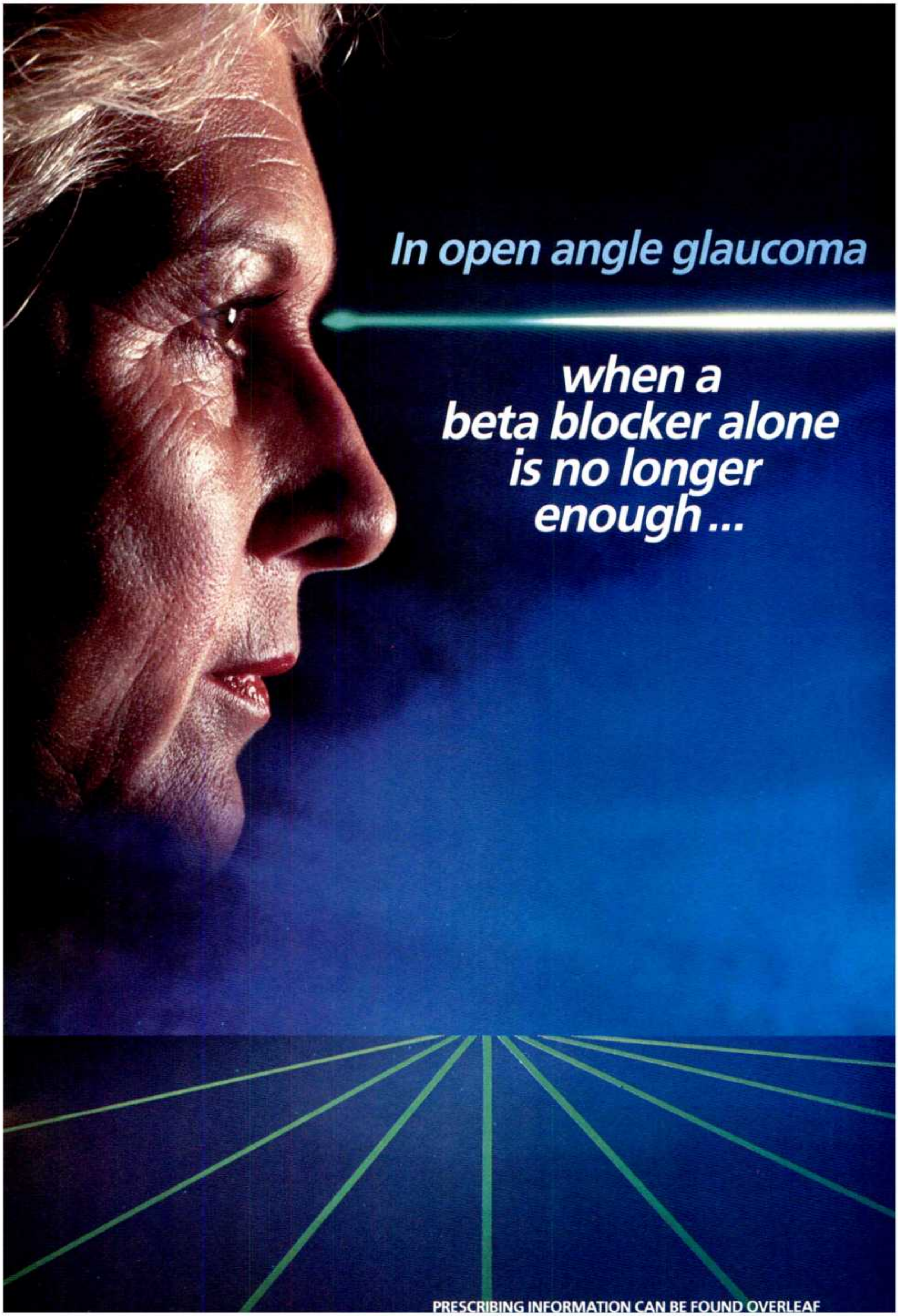
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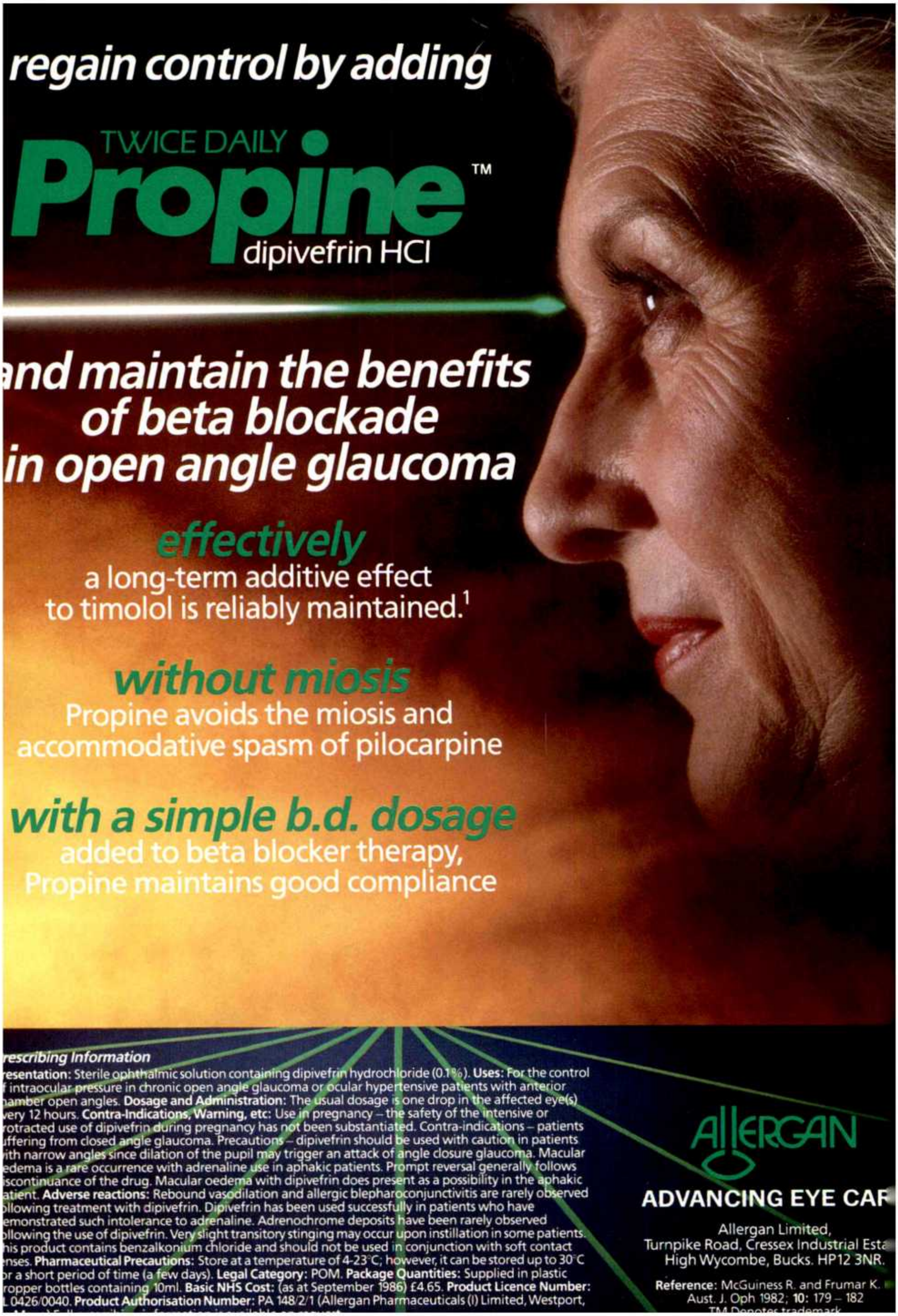

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British Journal of Ophthalmology, 1988, 72, 601–606

Long-term visual results after pars plicata lensectomy-vitrectomy for congenital cataracts

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SUMMARY We performed a pars plicata lensectomy-vitrectomy on 32 patients (47 eyes) with congenital cataracts. Ocular abnormalities, mainly nystagmus, strabismus, and microphthalmia, were present in 29 patients. No complications occurred intraoperatively or postoperatively in 39 eyes with up to 8½ years' follow-up (average 2·2 years). The pars plicata approach is a good surgical technique for the management of congenital cataracts.

Congenital and early developmental cataracts have resulted in a large percentage of cases of childhood blindness.[1,2] The surgical management of such eyes has been debated in the literature for over 50 years. Early techniques such as discission, linear extraction, and intracapsular extraction were plagued by a persistently high rate of surgical complications.[3-7] More recently the discission and aspiration technique for congenital cataracts has been advocated.[8-11] However, the incidence of complications with this technique, including vitreous loss, secondary glaucoma, retinal detachment, and, in particular, secondary membrane formation, remains quite high. Despite the use of phacoemulsification instruments, postoperative complications often necessitated additional procedures during the critical period of visual development.[12-14]

A major innovation in the management of congenital cataracts has been the application of automated vitrectomy instruments.[15,16] Both translimbal and transciliary body approaches are in use.[17-19] While the anterior segment approach through the limbus may effectively produce an optically clear visual axis, the procedure is complicated by a high incidence of cystoid macular oedema and by vitreous incarceration in the limbal incision.[20,21] We have performed pars plicata lensectomy-vitrectomy in congenital cataracts for over 12 years with good surgical results and a low incidence of postoperative cystoid macular oedema.[22-26] This report describes the long-term visual outcome of infants and juveniles who have had congenital and developmental cataracts managed with this approach.

Material and methods

Thirty-two patients (47 eyes) were referred to the vitreous service of the University of Illinois Eye and Ear Infirmary between 1974 and 1986. Six patients between the ages of 5 weeks and 18 years had a unilateral cataract. In only one was an autosomal dominant mode of inheritance suggested by family history; no aetiology was identified for the remaining five patients.

Twenty-seven patients between the ages of 3 weeks and 10 years had bilateral cataracts. Bilateral lensectomy-vitrectomy was performed in 15, while 10 of the remaining 11 patients underwent another procedure on the contralateral eye. In five patients the congenital cataracts were attributed to maternal infection with rubella. All five also had microphthalmia. Three of these patients had valvular heart defects, deafness, and mental retardation as well. Three patients had dominantly inherited congenital cataracts. In addition one patient had Down's syndrome, another had mental retardation and a seizure disorder, and a third was diagnosed with Peters' anomaly. Among the other patients one was born with raised titres to cytomegalovirus; one had a congenital herpesvirus infection resulting in hydrocephalus, severe mental retardation, and cataracts; and one had microphthalmia with cataracts and multiple craniofacial anomalies.

Before surgery, whenever possible, all eyes were

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examined for corneal size, intraocular pressure, clarity of the media, and visual acuity. Muscle balance and the presence of nystagmus were noted. None had undergone previous surgery. All procedures were performed with the patients under general anaesthesia.

SURGICAL PROCEDURE

The eye was maximally dilated preoperatively. After surgical preparation and sterile draping 4–0 black silk sutures were used to retract the eyelids. The conjunctiva was opened through a limbal peritomy, and bridle sutures were placed beneath the rectus muscles. In infants a 3·5 mm long sclerotomy was made 2·0 to 2·5 mm behind and parallel to the limbus with a no. 67 Bard-Parker blade. In older children the sclerotomy was made 3 mm from the limbus.

The ciliary body was exposed at the sclerotomy site and gently diathermised. A 5–0 polyglactin 910 (Vicryl) or 7–0 polyfilament (Supramid) mattress suture was passed through the sclerotomy and tied with a loose double-throw knot. A 52-s Beaver blade was inserted into the lens with a slicing motion and removed for insertion of a wide-angle Peyman vitrophage.[27] If the blade did not easily penetrate the centre of the lens (rare in children), a Peyman lens fragmentor was used to pulverise the lens nucleus for about 60 seconds.[28] The wide-angle cutter was placed in the eye, the knot was tightened, and the lens material was cut and aspirated. The lens capsule was not removed until the entire nucleus and cortex were aspirated. The lens material behind the iris was sucked into the vitrophage and brought into the pupillary space to be cut and removed, followed by the anterior and posterior capsule.

If the pupil did not dilate, a sector iridectomy was performed with the vitrophage. An anterior vitrectomy was preceded by a deep vitrectomy confined to the central core down to the optic disc. A modified Goldmann posterior pole lens and an operating microscope were used for direct visualisation. The vitrophage was then removed, and the scleral mattress suture was tightened until the sclerotomy was watertight. If the eye was soft, intraocular pressure was re-established with an injection of normal saline solution through the sclerotomy site into the vitreous chamber with a 30-gauge needle. The conjunctiva was closed with 6–0 plain catgut, and atropine and Maxitrol (neomycin, polymixin B, and dexamethasone) drops were instilled, and patch and shield were placed.

Results

Our follow-up has ranged from one week after discharge to 11 years (average 2·2 years). Nineteen of our patients were seen for follow-up at our institution for less than two years. However, the median visual acuity of those receiving visual rehabilitation for at least two years was 20/100. The patients' best corrected visual acuities were recorded preoperatively and at the time of the last visit.

No surgical or postoperative complications occurred in 39 eyes. Two patients had transient corneal oedema postoperatively that resolved spontaneously over several days. One patient had transient corneal oedema and intravitreal bleeding from the iris. The child with Down's syndrome had bilateral cystoid macular oedema noted by fluorescein angioscopy four months postoperatively, which cleared by 32 months. One case of increased intraocular pressure and iritis in the immediate postoperative period responded to acetazolamide and steroid drops. Three months postoperatively this patient suffered a retinal detachment that was treated successfully with a scleral buckle and cryotherapy. One eye had a retinal dialysis intraoperatively. Another patient had a retinal detachment two weeks postoperatively; both conditions were treated successfully. No other retinal detachments were observed up to 8½ years after pars plicata lensectomy-vitrectomy (Table 1).

Of the 10 patients whose contralateral eye had a procedure other than the pars plicata lensectomy-vitrectomy, five had secondary membrane formation. Discission and aspiration in one such case resulted in increased intraocular pressure, choroidal atrophy, and fibrous ingrowth of the cornea; postoperative visual acuity was light perception. The right eye, which underwent a pars plicata lensectomy-vitrectomy, suffered no complications; postoperative visual acuity was 20/60.

None of the patients whose contralateral eye had an alternative procedure had a better final visual acuity in that eye than in the eye that had pars plicata lensectomy-vitrectomy (Table 2).

Results of the long-term outcome in our monocular cases are hindered by a lack of follow-up information However, the children with acquired monocular cataracts who were operated on at ages 4, 18, and 10 years, respectively, showed an improvement of 5 and 6 lines on the Snellen chart in two cases and from counting fingers to 20/50 in the third. There was one case of a choroidal detachment postoperatively that resolved after six weeks (Table 3).

All but four patients with bilateral congenital cataracts had nystagmus, strabismus, or both. Two (patients 14 and 23) had a visual acuity of 20/200 preoperatively. One (patient 13) with central, steady, and maintained vision preoperatively was operated on after 3 years of age. Severe mental retardation in the fourth patient (patient 8) made accurate visual assessment difficult.

Table 1 *Bilateral congenital cataracts treated with pars plicata lensectomy-vitrectomy in both eyes*

Patient no	*Eye*	*Procedure**	*Age at surgery*	*Aetiology*	*Follow-up*	*Visual acuity†*		*Complications*	*Comments*
						Preop	*Follow-up*		
1	OD	PPLV	44 mo	Rubella	18 mo	No view	CNSNM	None	Pendular nystagmus
	OS	PPLV	44 mo			No view	CNSNM	None	
2	OD	PPLV	7 wk	Rubella	12 mo	No view	CNSM	None	Fine pendular nystagmus
	OS	PPLV	10 wk			No view	CNSM	Transient corneal oedema	Right esotropia
3	OD	PPLV	4 5 yr	Rubella	1 wk	No view	LP	None	Pendular nystagmus
	OS	PPLV	4·5 yr			No view	LP	None	Right esotropia
4	OD	PPLV	6 mo	Autosomal	6 yr	No view	20/60	Transient corneal oedema	Occlusion nystagmus
	OS	PPLV	8 mo	dominant		No view	20/60	None	Left estropia, high myopia
5	OD	PPLV	13 wk	Idiopathic	4 mo	No view	CNSM	None	Pendular nystagmus
	OS	PPLV	16 wk			No view	CNSM	None	
6	OD	PPLV	13 wk	Idiopathic	4 mo	No view	CNSM	Retinal dialysis	Pendular nystagmus
	OS	PPLV	16 wk			No view	CNSM	None	
7	OD	PPLV	11 mo	Idiopathic	5 mo	No view	CNSM	None	Fine pendular nystagmus
	OS	PPLV	9 mo			No view	CNSM	None	
8	OD	PPLV	12 wk	Herpesvirus,	2 yr	No view	CSM	None	Straight without nystagmus
	OS	PPLV	9 wk	retardation		No view	CSM	None	
9	OD	PPLV	10 mo	Autosomal	1 yr	No view	CSM	None	Left esotropia
	OS	PPLV	8 mo	dominant		No view	CSM	Retinal detachment	
10	OD	PPLV	14 wk	Idiopathic	6 mo	No view	CNSM	None	Pendular nystagmus
	OS	PPLV	16 wk			No view	CNSM	None	
11	OD	PPLV	9 wk	Cytomegalovirus	4 5 yr	No view	20/60	None	Fine pendular nystagmus
	OS	PPLV	10 wk			No view	20/60	None	Right esotropia
12	OD	PPLV	8 yr	Retardation,	3 yr	20/400	20/100	None	Nystagmus
	OS	PPLV	10 yr	seizures		20/400	20/100	None	Alternating exotropia
13	OD	PPLV	37 mo	Idiopathic	2·5 yr	CSM	20/100	None	Straight without nystagmus
	OS	PPLV	40 mo			CSM	20/100	None	
14	OD	PPLV	5 yr	Idiopathic	1 yr	20/100	20/30	None	Straight without nystagmus
	OS	PPLV	4 5 yr			20/200	20/40	None	
15	OD	PPLV	8 yr	Idiopathic	3 yr	HM	20/200	None	Left exotropia
	OS	PPLV	9 yr			HM	HM	Retinal detachment, iritis	

*PPLV indicates pars plicata lensectomy-vitrectomy

†Preop indicates preoperative, CNSMM, central, but neither steady nor maintained fixation, CNSM, central, not steady, but maintained fixation, LP, light perception, CSM, central, steady, maintained fixation, HM, hand motion.

Discussion

The pars plicata approach is an advantage to the pars plana procedure in children.[illegible] An incision made in the pars plana of young children may increase the risk of retinal detachment. Because the pars plicata is further anterior from the vitreous base and ora serrata, the risk of retinal detachment is lessened. The pars plicata approach also has many advantages over the translimbal approach. The pars plicata is in the direct axis of the lens, allowing for more complete removal of lenticular material. In contrast to the limbal approach, the cornea is not manipulated during surgery. Deep visualisation of the fundus is possible with a modified Goldmann lens, and lens fragments in the vitreous can be removed, thus preventing persistent inflammation postoperatively. An extensive vitrectomy also prevents pupillary block glaucoma resulting from a vitreous prolapse into the anterior chamber. Lastly, the vitreous is removed without trauma to the iris, which has been a suspected cause of cystoid macula oedema.[illegible]

The visual outcome after surgery for congenital cataracts also depends on the age of the patient at surgery, the density of the lens opacity, the period over which the cataracts developed, the presence of nystagmus or other ocular abnormalities, and the postoperative management. In our population a large percentage of cataracts in infants and young children was not discovered until many months after birth. Only six (19%) of our patients had cataracts identified and operated on before 3 months of age. Recent studies by Gelbart and associates[30] and by Rogers and coworkers[31] emphasise the need for surgery to be performed in the first eight weeks of life to achieve optimal visual rehabilitation of infants with dense bilateral cataracts.

Although we could not determine the time over which the lens completely opacified, 12 eyes (67%) with no view of the fundus preoperatively had a visual acuity no better than central fixation by age 2½ years (Table 4). Conversely, eight eyes (53%) with incomplete cataracts and at least central fixation preoperatively had a preoperative visual acuity of 20/60

Table 2 *Bilateral congenital cataracts in which one eye had pars plicata lensectomy-vitrectomy and the contralateral eye another procedure*

Patient no	*Eye*	*Procedure**	*Age at surgery*	*Aetiology*	*Follow-up*	*Visual acuity†*		*Complications*	*Comments*
						Preop	*Follow-up*		
16	OD	PPLV	6 mo	Idiopathic	2 yr	No view	CNSM	None	Fine pendular nystagmus
	OS	D & A	5 mo			No view	NCNSNM	Posterior capsular plaque	Intermittent left exotropia
17	OD	PPLV	31 wk	Down's	6 yr	No view	CNSNM	Cystoid macular oedema	Nystagmus
	OS	D & A	32 wk	syndrome		No view	CNSNM	Cystoid macular oedema	Right esotropia
18	OS	PPLV	3 wk	Rubella	3 yr	No view	20/100	None	Fine pendular nystagmus
	OD	I & A	4 wk			No view	20/100	None	
19	OS	PPLV	1 yr	Multiple	1 wk	No view	Clear view	None	Pendular nystagmus
	OD	I & A	9 mo	anomalies		No view	Clear view	Secondary membrane	
20	OD	PPLV	12 mo	Peters'	16 mo	No view	CNSNM	None	Coarse pendular nystagmus
	OS	Sector	15 mo	anomaly		No view	CNSNM	None	
21	OD	PPLV	4·5 yr	Rubella	1 wk	LP	LP	Transient corneal oedema	Pendular nystagmus
	OS	None				LP	LP	Bleeding iris	Right esotropia
22	OD	PPLV	4 yr	Autosomal	11 yr	No view	20/60	None	Left esotropia
	OS	D & A	8 mo	dominant		No view	LP	Glaucoma, fibrous ingrowth	
23	OS	PPLV	9 yr	Idiopathic	7 yr	20/200	20/40	None	High myopia, straight
	OD	D & A	7 yr			20/200	20/60	Secondary membrane	without nystagmus
24	OD	PPLV	5 yr	Idiopathic	None	20/80	20/40	None	Left exotropia
	OS	Phaco	5 yr			20/400	20/200	None	
25	OD	PPLV	1 yr	Idiopathic	8 5 yr	CSM	20/100	None	Pendular nystagmus
	OS	Phaco	1 yr			CSM	20/400	Secondary membrane	Left exotropia
26	OS	PPLV	22 mo	Idiopathic	5 yr	CSM	20/30	None	
	OD	D & A	16 mo			CSM	20/40	Secondary membrane	Right exotropia

*PPLV indicates pars plicata lensectomy-vitrectomy, D & A, discission and aspiration, I & A, irrigation and aspiration, Phaco, phacoemulsification

†Preop indicates preoperative; CNSM, central, not steady, but maintained fixation, NCNSNM, neither central, steady, nor maintained fixation, CNSNM, central but neither steady nor maintained fixation, LP, light perception, CSM, central, steady, maintained fixation, HM, hand motion.

Table 3 *Monocular congenital cataracts removed by pars plicata lensectomy-vitrectomy*

Case no	*Age at surgery*	*Aetiology*	*Follow-up, mo*	*Visual acuity**		*Complications*	*Comments*
				Preop	*Follow-up*		
1	4 yr	Idiopathic	14	20/400	20/60	None	
2	5 wk	Idiopathic	4	No view	CNSNM	None	Variable esotropia
3	6 mo	Idiopathic	8	No view	CSM	None	Left esotropia
4	10 yr	Idiopathic	1	Count fingers	20/50	None	
5	18 yr	Idiopathic	1	20/200	20/40	None	
6	5 wk	Autosomal dominant	2	No view	Clear view	Choroidal detachment	

*Preop indicates preoperative, CNSNM, central but neither steady nor maintained fixation, CSM, central, steady, and maintained fixation

Table 4 *Age at surgery and visual results after pars plicata lensectomy-vitrectomy for total cataract (n=18)**

Final visual acuity	*Age*				
	0–3 Mo	*3–12 Mo*	*1–2 Yr*	*≥2 Yr*	*%*
Light perception	–	–	–	3	17
CSM fixation to 20/100	2	4	1	2	50
20/100–20/60	1	–	–	–	5
20/60	2	2	–	1	28

*Includes those patients with 'no view' preoperatively and follow-up past age 2½ years

Table 5 *Age at surgery and visual results after pars plicata lensectomy-vitrectomy for incomplete cataract (n=15)**

Final visual acuity	*Age, yr*				
	0–1	*1–2*	*2–4*	*>4*	*%*
Hand motion to 20/200				1	7
20/200–20/100				1	7
20/100–20/60		1	2	2	33
20/60–20/30		1		7	53

*Includes those patients with at least fixation capability preoperatively or better (Table 5). These results agree with the findings of François[32] that 50% to 70% of cases with complete congenital cataracts had a postoperative visual acuity of less than 20/200, while 35% to 87% of cases with incomplete congenital cataracts had a final visual acuity of greater than 20/60.

Nystagmus, the most common ocular abnormality associated with bilateral visual deprivation amblyopia, occurred in 17 (65%) of our patients.[4,5,30,32] None achieved a visual acuity of better than 20/60. Although the amplitude of the nystagmus decreased during follow-up in some cases, it never resolved completely. Gelbart and associates,[30] Rogers and associates,[31] and Parks[33] noted the development of pendular nystagmus in infants with bilateral congenital cataracts by 12 to 13 weeks of age. This may represent the critical period at which irreversible amblyopia begins.[34,35]

Strabismus occurred with bilateral congenital cataracts in 14 (54%) of our patients. Gelbart and colleagues[30] reported esotropia in 21 of 24 patients with congenital cataracts despite early surgery and a short interval between operations for each eye. A recent Russian study of children with bilateral aphakia demonstrated strabismus in 50 of 52 patients.[36] France and Frank[37] described a 58% incidence of esotropia preoperatively; an additional 21% were identified after lens aspiration, refractive correction, and patching therapy.

Our experience with monocular congenital cataracts removed by pars plicata lensectomy-vitrectomy has been limited However, our three children with incomplete cataracts and no strabismus at the time of surgery regained useful vision, a finding consistent with that in the literature.[38] Recently, Beller and Hoyt have reported good visual results in eight of 11 infants who were operated on within the first six weeks of life, corrected frequently with extended-wear contact lenses, and treated with careful patching monitored by visual evoked potentials.[39]

Despite advances in our understanding of amblyopia in animal models and in humans, the management of both monocular and binocular congenital cataracts remains a tremendous clinical challenge. We have performed pars plicata lensectomy-vitrectomy for congenital cataracts in 32 patients. All retained a large clear pupillary space for the follow-up period. As in other studies, ocular abnormalities, including nystagmus, strabismus, and microphthalmia, have contributed adversely to the visual outcome.[1,4,5,17,30–32,37] Our long-term results are comparable to those found in the literature.[1,9,10,13,30,32] Despite the risk of retinal detachment, the pars plicata approach is a good surgical technique for the management of congenital cataracts.

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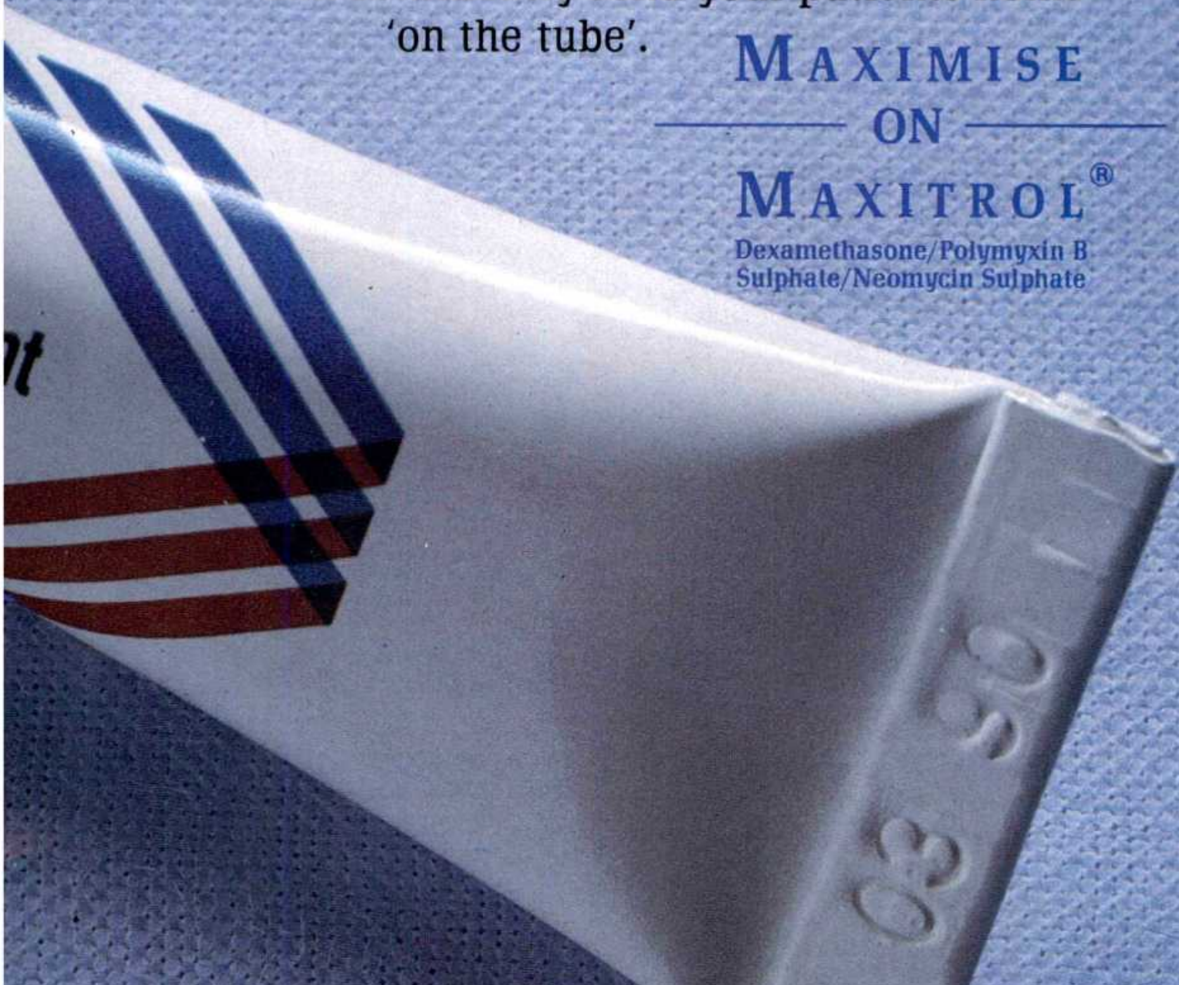

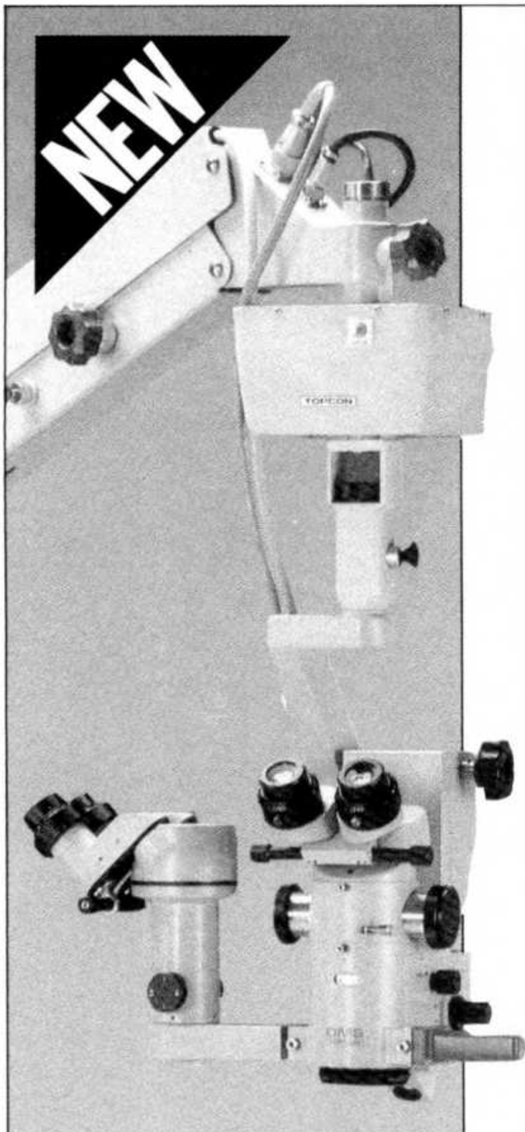

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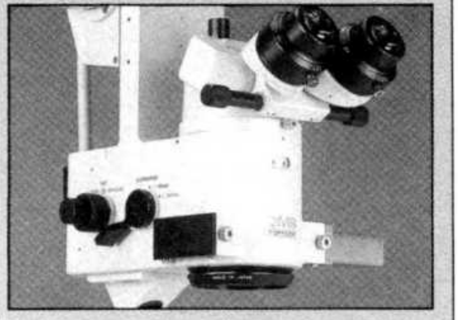

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A 10-year survey of penetrating eye injuries in Gwent, 1976–85

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SUMMARY A retrospective survey was performed of all penetrating eye injuries in Gwent from 1976 to 1985. It included 171 eyes. The results showed a gradual decline in all penetrating injuries and not just those due to road traffic accidents. An analysis of the cause and prognosis is given.

There have recently been several surveys of penetrating eye injuries in relation to the seat belt law which took effect in February 1983.[1-3] These cover short periods before and after the introduction of the law and examine only road traffic accident cases (RTAs). Other surveys before 1976 have examined periods of several years and categorised the type of injury most prevalent in the population at the time.[4-7]

The present survey was conducted to evaluate a clinical impression that apart from the fall in RTA injuries there has been a gradual decline in the number of penetrating injuries generally over the last few years and to examine any changing pattern of aetiology. The survey was conducted by examining the notes of all patients requiring surgery for penetrating injuries at St Woolos Hospital, Newport, Gwent. This is the sole unit for inpatient ophthalmic care in Gwent and has a current catchment population of 440 000.

Materials and methods

The survey included 171 eyes of 169 patients and covered the period 1 January 1976 to 31 December 1985. Patients were included in the study by examination of the operation books for this period and tracing the notes of all cases relating to ocular injury. Only those with penetrating injury were then included in this study. For each patient the age, sex, eye injured, aetiology, surgery, and final visual outcome were recorded, where available. Four sets of notes were not found (Table 1). These cases have not been included in any of the figures.

Results

Age and sex. There was a marked preponderance of male patients throughout the age range. The overall numbers were 147 males and 22 females, a ratio of approximately 7:1. Fig. 1 shows the age distribution of the two sexes and that the male incidence is highest in the second to fourth decades. The female incidence is highest in the first two decades. In three male patients the age was unrecorded. The right eye was involved in 82 cases (48%), and the left in 89 cases (52%).

Aetiology. In all but two cases the aetiology was recorded. In children play and sport were the commonest cause of injury, accounting for 79·2% of all cases under 16 years, with home accidents (14·6%) and assault (6·2%) accounting for the remainder (Fig. 2). Within the play and sport group are included 12 cases (25% of injuries under 16 years) due to darts, the commonest single factor in this group. Two of the cases over 16 years were also due to dart injuries. The incidence of dart injuries remained fairly constant throughout the survey and went against the general trend.

In adults industrial accidents were the commonest

Table 1 *Notes not traceable*

Year	*Sex*	*Description*
1977	Male	Left enucleation and facial suturing
1982	Male	Age 29, penetrating injury
1982	Male	Penetrating injury, prolapsed iris
1982	Male	Penetrating injury

Correspondence to W N Wykes, FRCS

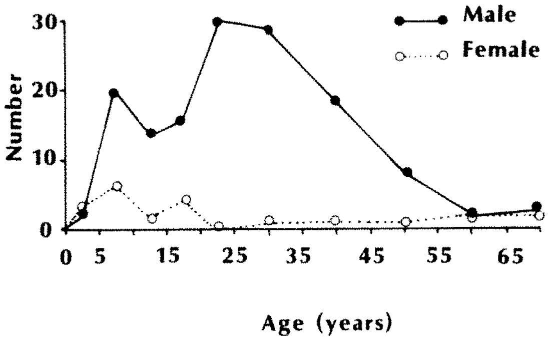

Fig. 1 *Distribution of injured patients by age and sex.*

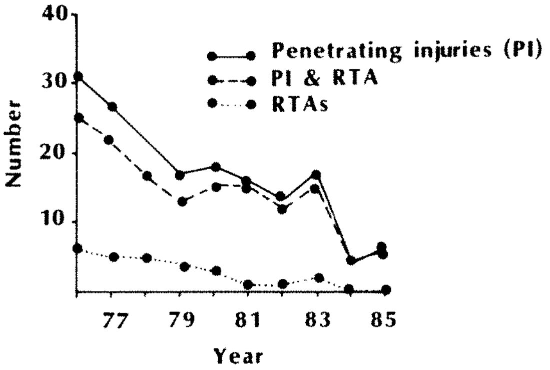

Fig. 3 *Penetrating injuries and road traffic accidents.*

cause, accounting for 53% of all cases over 16 years, while RTAs accounted for 21·3%, mainly in the 16–24 age group (68% of RTAs) (Fig. 2). The remainder were due to home accidents (12%), adult sport (6%), and assault (7·7%). In three cases—one RTA and two industrial accidents—the age was unknown.

Temporal trends. One of the main aims of the survey was to see whether there was a gradual decline in injuries apart from RTAs. The seat belt law came into effect during the time period of the survey. Fig. 3 shows the total number of penetrating injuries for each year and the number minus those due to RTAs. This shows a steady decline in all injuries, particularly in 1984 and 1985, and shows the same trend when the RTA figures are removed. The RTA cases themselves show a steady decline before the seat belt law was introduced, and only two cases since, both in late 1983.

There was a steady decline in industrial accidents during the 10-year period (Fig. 4, Table 2). There has also been some decline in play and sport injuries among children. However, the injuries due to darts (14 injuries, 12 in children under 16 years) show no trend. The injuries due to adult sport and assault show no overall trend (Table 2).

Visual prognosis. Examination of the final visual acuities revealed that nearly half the eyes (43·3%) regained a visual acuity of 6/12 or better (Table 3). However, almost a quarter (24·5%) of the patients were completely blind—that is, had no perception of light (6·4%)—or had the eye enucleated (18·1%).

Primary enucleation was performed in three cases owing to extensive injuries. The indications for the remaining 28 enucleations are given in Table 4. Of the causes of injury in the total of 31 enucleations play and sport (8) and industrial accident (8) were the commonest, with RTA (4), home accident (4), assault (4), and adult sport (3) accounting for the rest. Five of six eyes injured by airguns were enucleated, reflecting the severity of this type of

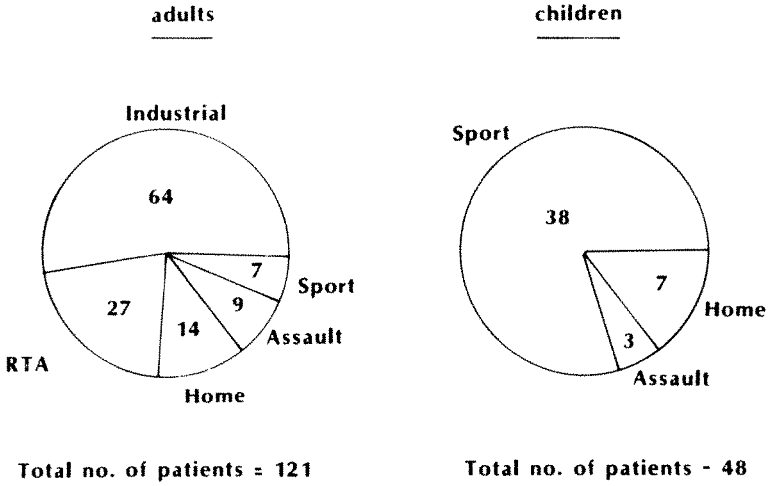

Fig. 2 *Aetiology of ocular injury.*

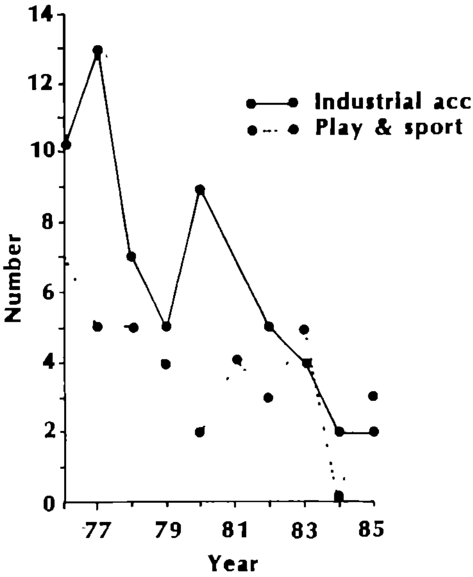

Fig 4 *Trends: industrial accidents play and sport*

injury. Eleven of the eyes enucleated were in patients under 16 years old.

Sympathetic ophthalmitis occurred in four patients, one of whom, aged 6, presented with sympathetic ophthalmitis after a dart injury 10 days earlier. Of the other three, one had been involved in an RTA, one had been hit by a steel band at work, and one had been hit by a piece of wood.

Further operations. Seventy-six eyes (44·4%) underwent further surgery, some having as many as four operations in all (Table 5). Cataract extraction (29·6%) and enucleation (25·9%) were the commonest operations. Other operations included trabeculectomy, resuturing of the conjunctiva after enucleation, and plastic surgery of the lids.

Intraocular foreign bodies Thirty-seven cases (21·6%) were of retained intraocular foreign bodies. Hammering injuries accounted for over half (56·8%) of these (Table 6). A further fifth (18·9%) were due to various causes involving small fragments of metal.

Discussion

The incidence of penetrating eye injuries due to RTAs has been shown to have fallen since the introduction of the seat belt law on 1 February 1983.[1–3] Vernon and Yorston[1] reported a 58% reduction in two six-month periods before and after the law, and Hall *et al.*[2] found a 73% reduction comparing a two-year period before and after the law. Johnston and Armstrong[3] reported a 60% reduction in Northern Ireland over the same period. However, the present survey indicates a steady decline in RTA injuries over the years preceding the law, with only two cases since. This may reflect a response to the publicity campaigns preceding the law and the controversy and resultant attention of the media surrounding the law itself.

A major purpose of the survey was to investigate the clinical impression that the number of penetrating injuries seen annually was steadily decreasing, apart from the reduction in RTAs. This is shown to be the case when the injuries due to RTAs are removed from the figures, in contrast to the figures produced by Johnston and Armstrong,[3] who found that in 1981–3 there were 89 injuries from causes other than RTAs compared with 94 in 1983–5. The decline shown in this survey is mainly due to the decrease in injuries from industrial accidents, though there has been a slight decline in play and sport injuries among children.

In 1923 Garrow[4] reported that occupational injuries accounted for 70% of all eye injuries, but the Northern Ireland survey of 1967–76 found that only 15·4% were industrial and that this rate was fairly constant over the 10 years.[5,6] Johnston and Armstrong reported that 14% of perforating injuries without intraocular foreign body and 72% with

Table 2 *Cause of injury by year*

	Industrial accident	*Play/sport (children)*	*RTA*	*Home accident*	*Assault*	*Adult sport*	*Unknown*	*Total*
1976	10	7	6	3	2	3	–	31
1977	13	5	5	1	3	–	–	27
1978	7	5	5	4	–	1	–	22
1979	5	4	4	2	1	1	–	17
1980	9	2	3	4	–	–	–	18
1981	7	4	1	3	–	1	–	16
1982	5	3	1	–	2	–	2	13
1983	4	5	2	4	2	–	–	17
1984	2	–	–	–	1	1	–	4
1985	2	3	–	–	1	–	–	6
Total	64	38	27	21	12	7	2	171
%	37·4	22·2	15·8	12·3	7·0	4·1	1·2	100

Table 3 *Final visual acuity*

Acuity	*No*	*%*
6/6 or better	36	21 1
6/7 5–6/12	38	22·2
6/18–6/36	16	9·4
6/60 or worse	22	12 9
No perception of light	11	6·4
Enucleation	31	18·1
Unrecorded	17	9·9
Total	171	100

Table 4 *Indication for enucleation*

	No	*%*
Eye damaged beyond repair	3	9·7
Blind painful eye	23	74 2
Phthisis	3	9·7
Endophthalmitis	2	6·4
Total	31	100

Table 5 *Further operations*

Operation	*2nd op*	*3rd op.*	*4th op*	*Total*	*%*
Enucleation	23	4	1	28	25 9
Cataract extraction	29	3	–	32	29 6
Capsulotomy	6	8	2	16	14 8
Retinal detachment	5	3	1	9	8·4
Squint	2	5	–	7	6·5
Other	11	3	2	16	14·8
Total	76	26	6	108	100

Table 6 *Intraocular foreign bodies*

Cause	*No.*	*%*
Hammer and chisel	17	46 0
Hammer and nail	4	10 8
Metal from unknown cause	7	18 9
Airgun pellet	2	5 4
Shotgun pellet	2	5·4
Plaster	2	5·4
Other	3	8·1
Total	37	100

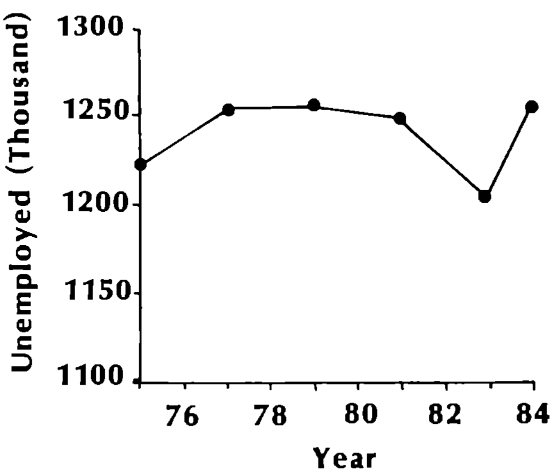

Fig. 5 *Unemployment in Wales*

were industrial.[3] In this survey of penetrating injuries 37·4% were industrial, but this reflects a reduction in other causes rather than an increase in industrial accidents, and the decline during the 10 years is heartening.

The male/female ratio of 6·68:1 is in keeping with other surveys. Canavan *et al.*[6] found a ratio of 5·25:1, and Blomdahl and Norrell[7] found a ratio of nearly 6:1.

In those patients whose visual outcome was known 43·3% had a final visual acuity of 6/12 or better, compared with a range of 21–68% in other studies; 24·5% were rendered completely blind (including those with enucleated eyes) compared with 12·2–31%, and the enucleation rate was 18·1% compared with 9·2–28%.[4,5,7,8] Of the enucleated eyes a third (35·5%) related to children, five being due to air rifle injuries and two to dart injuries. Overall, darts accounted for 14 injuries, 12 of them in patients under 16 years, and this was the commonest single cause of injury in children.

Four cases of sympathetic ophthalmitis occurred of which one already had sympathetic involvement on presentation. Johnston[4] found two cases in his survey of 376 cases despite the excision rate of 28%. Therefore, although the incidence is low, sympathetic ophthalmitis is still a real danger which must be borne in mind when treating penetrating injuries.

The possibility that the decline in industrial injuries was due to a fall in employment was considered. Specific figures for unemployment in Gwent were not available over the period, but the unemployment figures for Wales do not show any correlation with the decline in injuries (Fig. 5).[11] However, there may have been a shift in the type of employment away from heavy engineering.

CONCLUSION

This survey has shown a gradual decline in all penetrating injuries over the 10-year period from 1976 to 1985, not simply a reduction in RTA cases. The major causes throughout are industrial accidents in adults and play and sport in children. Both groups show a decline in incidence over the period which is particularly marked in the case of industrial injuries. Among the children dart injuries are the single most common cause and they do not show any decline in frequency, which is most distressing. They are clearly not subject to the same factors involved in the general decline, and perhaps specifically drawing attention to this problem in the media would help.

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Choroidal osteoma presenting in pregnancy

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SUMMARY A case of choroidal osteoma presenting during pregnancy is reported. The clinical findings are summarised and the features of choroidal osteoma are discussed.

A 32-year-old woman presented with a history of occasional blurring of vision of the left eye over the period of 10 weeks. These attacks had lasted for a few minutes and cleared, leaving her with no visual defect. During the month prior to presentation, however, she had noticed a persistent blurring of the central vision. There was no relevant medical history apart from the fact that she was in the third month of an uncomplicated pregnancy.

Her corrected visual acuities were 6/4 in the right eye and 6/6 in the left eye. The left visual field showed a relative scotoma extending from the blind spot towards fixation. Examination of the right eye showed it to be entirely normal, but the left eye had a flat, well circumscribed, yellowish, mottled, juxtapapillary lesion extending from the inferior aspect of the disc upwards to involve the macula (Fig. 1). Fine tufts of irregular vessels were seen on the surface of the lesion.

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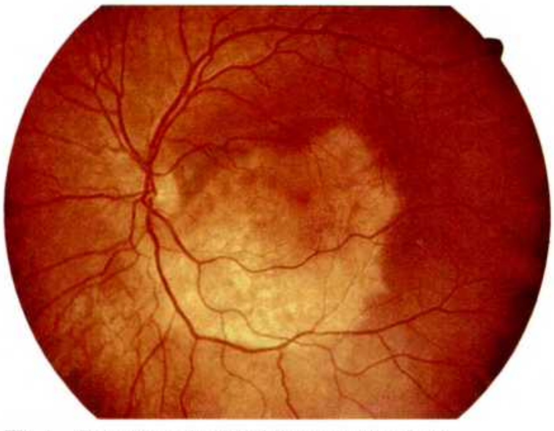

Fig. 1 *Posterior pole of the left eye showing large juxtapapillary choroidal lesion.*

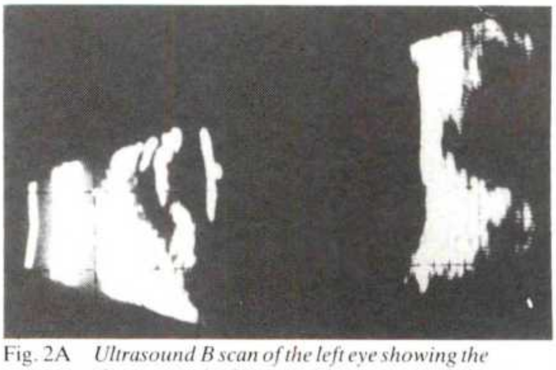

Fig. 2A *Ultrasound B scan of the left eye showing the tumour with acoustic shadowing of the structures behind it.*

Ultrasound B scan showed an acoustically dense choroidal mass at the posterior pole which caused an acoustic shadow. On reduction of the gain which suppressed all other posterior wall echoes, a strong echo persisted from the mass (Figs. 2A, B). The patient was kept under regular review, but no other investigations were performed until she had given birth at term. On re-examination a slight increase in the size of the lesion was noted, but the visual acuity and the scotoma remained static. A fluorescein angiogram showed early patchy hyperfluorescence of the lesion, which persisted into the later stages of the angiogram. A CT scan showed a radiodense lesion

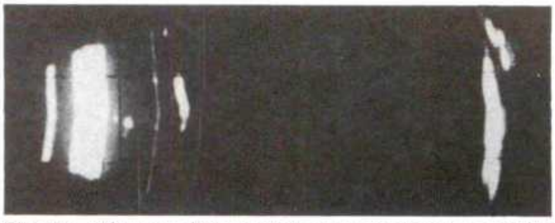

Fig. 2B *Ultrasound B scan of the same eye showing a highly reflective tumour at low ultrasonic intensity.*

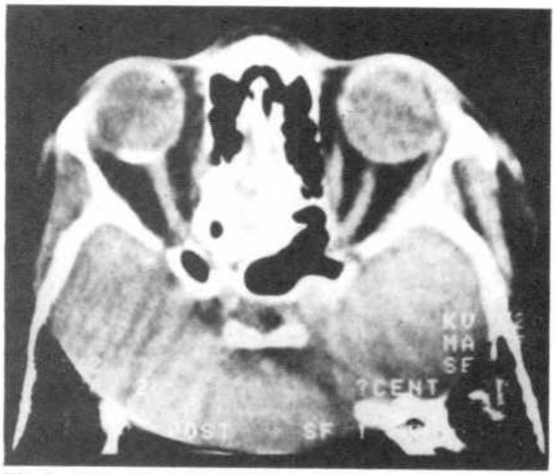

Fig. 3 *Computerised axial tomography scan showing the presence of a bony plaque at the posterior pole of the left eye.*

adjacent to the left optic nerve head, and this had the same density as normal bone (Fig. 3). A diagnosis of choroidal osteoma was made. The patient has been followed up for over a year, with no further visual deterioration or enlargement of the lesion being demonstrated.

Discussion

CLINICAL FEATURES

The features of choroidal osteoma were described by Gass and Guerry[1] when they described four young female patients with similar juxtapapillary lesions and sharing similar clinical characteristics. In a separate report on one of these patients Williams and Fort[2] reported the pathological findings on one of the eyes enucleated for a suspected choroidal melanoma after a positive ^{32}P test.

Choroidal osteoma tends to occur in young females patients. In a series of 15 cases reviewed by Gass[3] 14 were female, with an age range of 8–36 and a median age of 20 years. Unilateral involvement is usual, with no preference for it to affect either eye having been found. However, bilateral involvement has been reported,[3] and multiple occurrences in a patient with recurrent orbital pseudotumour are known.[4]

Blurred vision and metamorphopsia are the main presenting features, and paracentral scotoma may be demonstrated. The visual acuity is usually good unless extensive macular complications have occurred. The lesions have an affinity for the juxtapapillary region and tend to have irregular borders and a geographic pattern, with a yellow-white or orange-red colour, depending on the degree of thinning of the retinal pigment epithelium. Multiple short tufts of branching vessels on the tumour surface arising from marrow spaces within the osteoma are said to be characteristic. The prompt perfusion of the choriocapillaris gives rise to diffuse mottled hyperfluorescence early in the fluorescein angiogram, and later patchy fluorescein staining may be due to filling of these marrow spaces where they communicate with the surface.

The typical ultrasound finding is that of an acoustically dense, slightly elevated choroidal mass which renders the tissue behind it anechoic, producing an apparent defect in the retrobulbar tissue. If the ultrasound gain is reduced, so that all the posterior wall echoes are suppressed, a high-amplitude echo persists from the osteoma. Orbital *x*-rays may show the radiodense lesion, which may be highlighted by polytomography. CT scan of the orbit will best show the lesion of the posterior pole of the eye with a density similar to that of bone.

NATURAL HISTORY

The visual acuity may be good, with minimal visual disturbance at first, but lesions near the macula may give rise to serous retinal detachment and subretinal neovascularisation. Of 14 eyes followed up for seven years Gass reported that eight maintained 6/12 vision while six fell to 6/60 or worse.[3]

HISTOPATHOLOGY

The features of two eyes studied after enucleation have been reported and another case reviewed, having been reported to be an ossified haemangioma by Reese.[4] The lesions were situated between the inner one-third and the outer two-thirds of the choroid, separated from the retinal pigment epithelium and Bruch's membrane by a thin layer of fibrous tissue. The retinal pigment epithelium showed patchy thinning and depigmentation but no hyperplasia, and in these areas of disruption rod and cone loss was found, with a layer of subretinal exudate. No evidence of haemangioma or changes suggesting the origin of the osseous tissue was found.

ORIGIN

The origin of choroidal osteoma is still a cause for discussion. Are they primary lesions, or is there an underlying stimulus for ossification? It is true that choroidal haemangiomas undergo osseous metaplasia, but this always occurs on the inner surface of the haemangioma in association with extensive degenerative and proliferative changes of the retinal pigment epithelium not seen in the osteomas examined so far. Heterotopic bone formation is seen in degenerated eyes following trauma, inflammation, and long standing retinal detachment. However, hyperplastic changes of the retinal pigment epithelium are usually seen, and the origin of the bone is thought to be due to metaplasia of the retinal pigment epithelium in response to degenerative changes. Choroidal haemorrhage and focal choroiditis, which might be implicated in bone formation, have not been reported in previous cases of choroidal osteoma and were certainly not a feature of the case reported in this paper. Katz and Gass[5] reported a case of multiple choroidal osteoma occurring in a 10-year-old girl with recurrent orbital pseudotumour, and during the period of active growth of the choroidal lesions they recorded transient elevation of the serum parathyroid hormone level and alkaline phosphatase. But there are few other recordings of an underlying metabolic disorder, and routine biochemical studies have been found to be unhelpful.

The optic nerve head has a complicated embryological development and is a common site for developmental tumours such as melanocytomas, astrocytic hamartomas, and choroidal haemangiomas. However, choroidal osteomas show features atypical of developmental tumours, such as their exclusive location in the juxtapapillary choroid, their occurrence predominantly in females, and their capacity for growth in later life. Some authorities now believe that the structure of the osteomas and their ability to develop in previously unaffected eyes indicate that they develop from reactive metaplasia of mesenchymal or retinal pigment epithelial cells. The stimulus for this reaction is not clear, but since the lesions occur predominantly in females a hormonal influence has been postulated.[1,4] During pregnancy there is a marked modification of the endocrine environment and the metabolism—for example, the increase in plasma oestrogen, which has a general protein anabolic effect and is thought to have a specific stimulatory effect on the activity of osteoblasts. The patient presented here was in the first trimester of pregnancy when her permanent symptoms first occurred, and it would be attractive to postulate that the increased hormonal activity might be implicated in the exacerbation of the choroidal osteoma.

I thank Mr J Thornitt for permission to report this case and Miss K Jones for the photography

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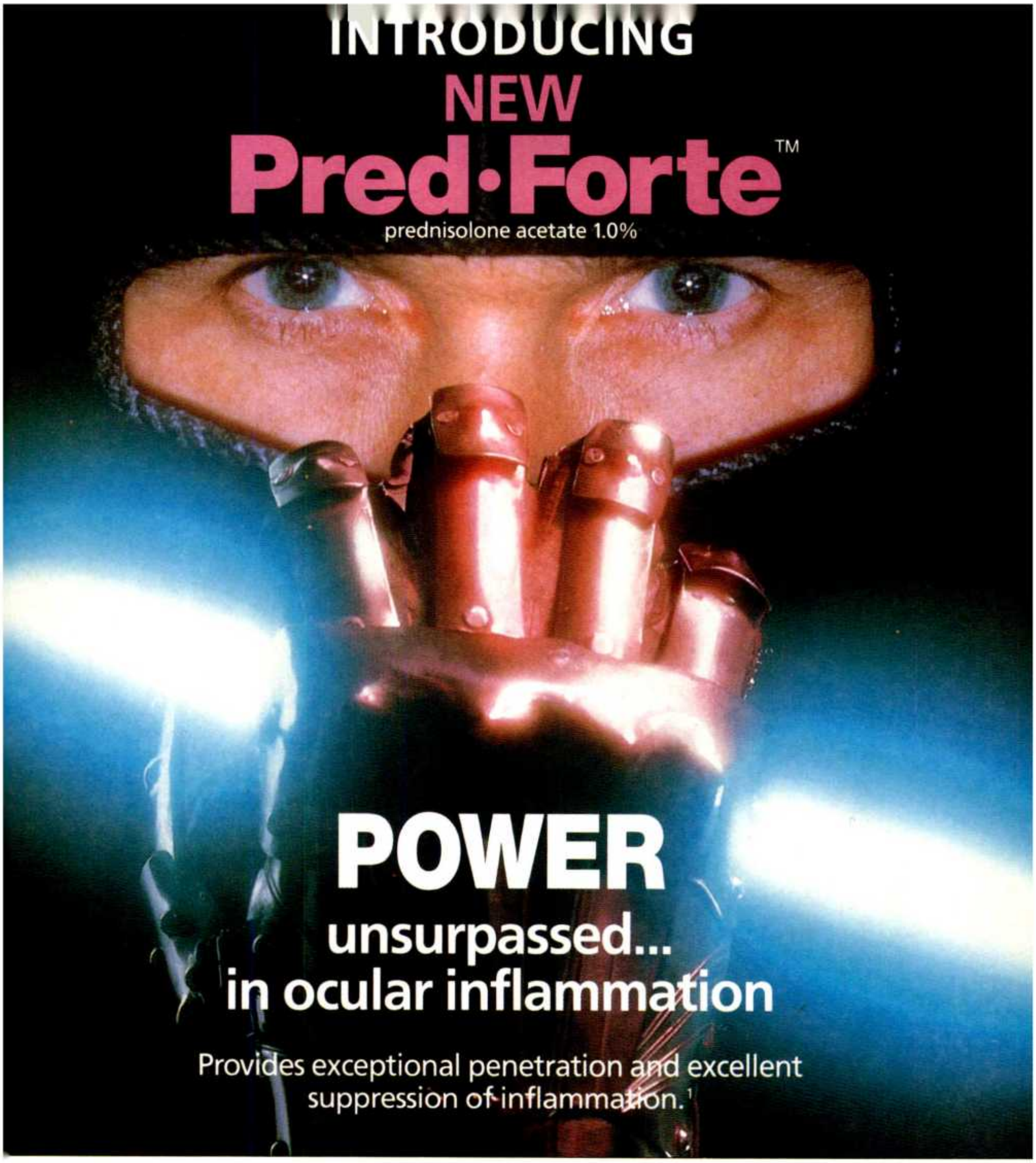

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British Journal of Ophthalmology, 1988, 72, 615–617

Short-term effects of neodymium-YAG transscleral cyclocoagulation in patients with uncontrolled glaucoma

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SUMMARY Transscleral Nd-YAG cyclocoagulation has been reported to lower intraocular pressure (IOP) in animals, eyes and more recently in human eyes. We treated 14 patients with uncontrolled IOP using this technique. Three patients were lost to follow-up. The mean follow-up time was 12 (SD 2·6) weeks. There was a decrease in IOP in all patients. Seven patients had final IOP readings ≤25 mmHg (63·6%). Six patients had IOP ≤21 mmHg (54·5%). Fairly severe complications occurred in most patients. None, however, developed phthisis bulbi. Two patients had one treatment (18%), eight patients had two treatments (72%), and one patient had three treatments (9%). This preliminary study confirms that Nd-YAG cyclocoagulation effectively lowers IOP in patients with uncontrolled glaucoma over the short term.

Beckman *et al.* reported that trans-scleral ruby laser treatment of the ciliary body lowers IOP in both animals and human eyes by causing destruction of the ciliary body.[1 2] In 1985 Wilensky *et al.* reported that trans-scleral Nd-YAG cyclocoagulation can be used to decrease IOP in rabbits.[3] This effect has recently been confirmed by Devenyi *et al.*[4]

The purpose of this pilot study was to determine whether trans-scleral Nd-YAG cyclocoagulation can lower IOP in patients with uncontrolled glaucoma

Material and methods

Prior to the start of this study a recently enucleated human cadaver eye was treated with Nd-YAG laser 2–3 mm from the limbus with energy levels as indicated below. This eye was then studied histopathologically to ensure that the laser was focused in the region of the ciliary processes.

Fourteen patients with uncontrolled IOP were treated with the trans-scleral Nd-YAG (thermal mode) cyclocoagulation as follows. All patients were admitted to hospital. All received a complete physical and ocular examination which included visual acuity, slit-lamp, Goldmann applanation tonometry, gonioscopy, and funduscopy. Informed consent was obtained from all patients

Of the 14 patients treated 10 had neovascular glaucoma (NVG), three had secondary angle closure glaucoma (2nd ACG), and one had aniridia.

All patients were given retrobulbar anaesthesia with 3–4 ml xylocaine 2% bupivacaine 0·5% mixture 15 minutes before the treatment. A lid speculum and tooth forceps were used to keep the eye open and to move the eye so that the laser beam could be applied as perpendicular to the sclera as possible.

The Lasag Microruptor-2 neodymium-YAG laser

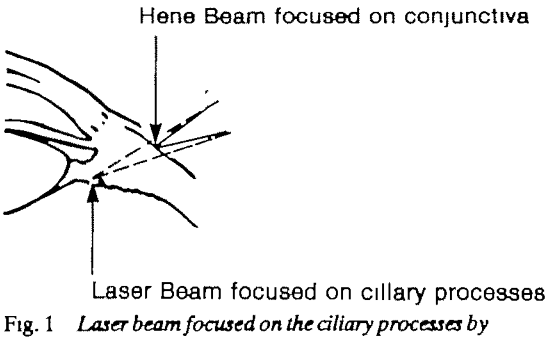
Hene Beam focused on conjunctiva
Laser Beam focused on ciliary processes

Fig. 1 *Laser beam focused on the ciliary processes by offsetting the machine '9'.*

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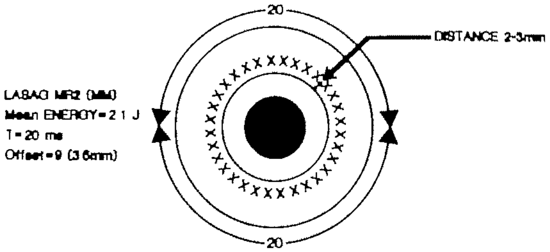

Fig. 2 *Location and number of Nd-YAG laser burns in relation to the limbus.*

set in the thermal mode was used. The mean energy was 2·10 joules (1·98–2·25 J) at 20 ms. The Hene beam was focused on the conjunctival surface with the offset at '9' (Fig. 1). The mean number of laser burns given to each patient was (40±2), 2–3 mm from the limbus as measured with a caliper through 360° (Fig. 2).

The patients' mean age was 58·7 years (32–80 years). Six patients were females and eight were males. Pretreatment visual acuity ranged from counting fingers at 1·5 m to no light perception.

Post-treatment therapy included Pred Forte (prednisolone) 3–4 hourly and atropine 1% twice daily. All pre-treatment antiglaucoma medications were continued. Pain medication was prescribed if required.

All patients had an ocular examination and IOP check 24 hours after treatment and were then discharged from the hospital. The follow-up protocol included weekly, monthly, three-monthly, and then six-monthly examinations.

If the IOP ≥30 mmHg after one month the treatment was repeated up to three times. If the IOP did not drop to below 25 mmHg after three treatments, this result was considered a treatment failure. Student's *t* test was used to compare pre-laser with post-laser IOP levels.

Results

Three patients were lost to follow-up. Fig. 3 shows the IOP response to treatment. As indicated seven patients (63·6%) had IOP ≤25 mmHg. Six patients (54·5%) had an IOP drop ≤21 mmHg.

Fig. 4 shows the mean pre-laser and post-laser IOPs for the treated group as a whole. As indicated, there was a substantial drop in IOP from 48·5 mmHg to 24·2 mmHg, which was statistically significant.

The success rate differed according to the type of glaucoma. It was 57% for NVG and 75% for the others.

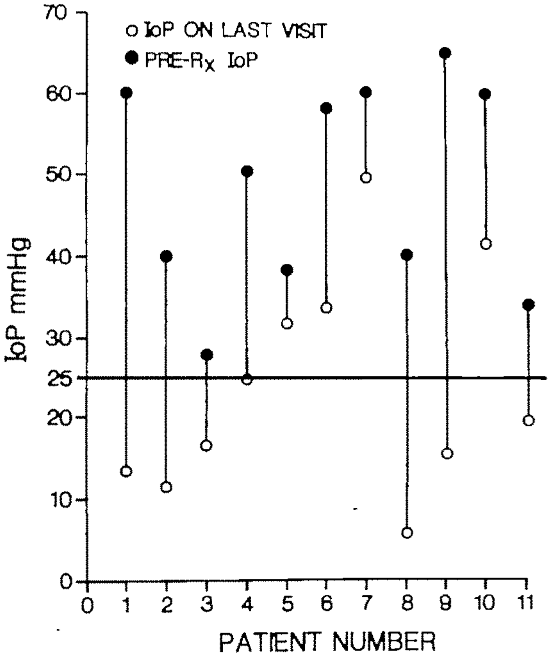

Fig. 3 *IOP readings before and after Nd-YAG laser treatment R_x=treatment*

Of the 11 patients studied, two received one treatment, eight received two treatments, and one had three treatments The mean follow-up time was 12·0 (SD 2·6) weeks.

Post-treatment visual acuity remained the same in eight patients, improved in two patients, and deteriorated in one patient owing to development of a dense cataract.

Table 1 lists the complications seen in the eleven patients As indicated, all patients developed corneal oedema, conjunctival injection, and iritis after treatment. Pain and gas bubbles in the anterior chamber were seen in five patients. Hypopyon developed in

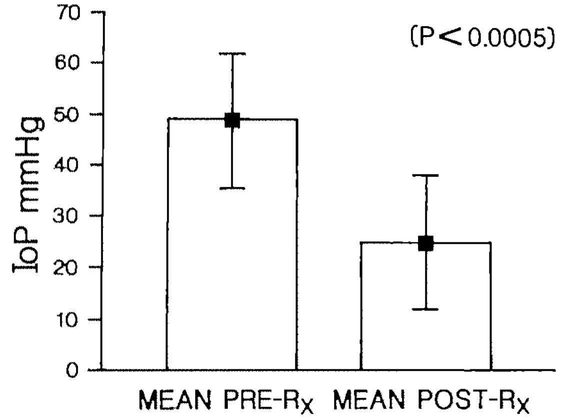

Fig. 4 *Mean pre- and post-treatment IOP R_x=treatment*

Table 1 *Complications in 11 patients*

Complications	*No of patients affected*
Corneal oedema	11
Conj injection	11
Iritis	11
Pain	5
Gas in anterior chamber	5
Hypopyon	4
Hyphaema	3
Cataract	1
Vitreous haemorrhage	1
Phthisis	0

four patients. Hyphaema developed in three patients. Cataract and vitreous haemorrhage developed in one patient. None of our patients developed phthisis bulbi over this time period.

Discussion

Uncontrolled glaucoma despite maximum medical therapy and failed filtration surgery remains a challenge to the surgeon. Many types of treatment are advocated, including cyclocryotherapy,[5] modified trabeculectomy,[6] seton implantation,[7] trabeculectomy with 5-fluorouracil,[8] and therapeutic ultrasound.[9] No method has proved to be entirely successful.

The Nd-YAG laser emits infrared light (wavelength 1064 nm). This has been shown to penetrate six times more deeply into tissues than argon laser before being absorbed.[10] The Nd-YAG in its thermal mode produces relatively low power outputs (100–200 W) owing to the long duration of the pulse (10–20 ms). During trans-scleral Nd-YAG cyclocoagulation the infrared energy penetrates the sclera, eventually being absorbed by the melanin in the ciliary processes' pigment epithelium. The light energy is converted to heat in this tissue, with damage of the ciliary processes. This results in decreased aqueous production, leading to a drop in IOP. Devenyi *et al.* recently reported that the sclera is not affected by this procedure.[4]

Our preliminary results show that trans-scleral Nd-YAG cyclocoagulation successfully decreases IOP in all patients with uncontrolled glaucoma. However, only 63·6% of patients had a drop in IOP to 25 mmHg or less. This result is similar to Beckman and Waeltermann's results with the ruby laser.[11]

Master *et al.* recently reported that 2·0 J/pulse is an adequate energy level to lower the IOP in patients with uncontrolled glaucoma without producing phthisis bulbi.[12] Our study confirms this. But larger numbers of patients and longer follow-up times are required before the ideal energy levels can be recommended.

Despite being treated with low energy levels all our patients developed complications. Many were mild, but one patient (with NVG) developed a vitreous haemorrhage and cataract. Whether this complication was due to the Nd-YAG laser or to the natural history of the disease is not clear

In conclusion, trans-scleral Nd-YAG cyclocoagulation appears to be an effective method of lowering the IOP in patients with severe uncontrolled glaucoma. It is, however, associated with significant complications. Long-term effects of this form of treatment on both IOP and ocular structures are not yet known.

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Cavernous haemangioma presenting as an orbital mass after enucleation for a choroidal melanoma: case report

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SUMMARY A patient presented with an ipsilateral orbital mass four years after enucleation for a choroidal malignant melanoma. Clinical examination revealed a darkly coloured mass suggestive of recurrent melanoma. CT scanning indicated a locally extensive tumour. Management was by excision without resort to orbital exenteration. Pathological examination revealed a cavernous haemangioma. The natural history of this tumour is discussed.

Cavernous haemangioma is the commonest primary orbital tumour.[1] Its pathogenesis is disputed, but it has been suggested that the neoplasm may become apparent only when growth takes place of a small, long-standing, or congenital pre-existing haemangioma.[2]

A case is reported in which a cavernous haemangioma arose in the orbit following enucleation of the ipsilateral eye for a uveal malignant melanoma. Intraoperative inspection of the socket during enucleation had revealed no evidence of an orbital tumour or vascular malformation.

Case report

A 63-year-old woman presented with sudden onset of blurred vision in the right eye. A thyroidectomy had been performed over 30 years previously for thyrotoxicosis, and there remained minimal lid retraction and lid lag on the right side, with slight proptosis. More recently she had developed Addison's disease, and had been treated with steroids. On examination the visual acuity in the right eye was 6/18 and in the left 6/9. In the right fundus there was a raised, lightly pigmented mass in the upper temporal quadrant above the macula, with an overlying serous retinal detachment. Systemic investigations revealed no evidence of a primary tumour elsewhere, and a diagnosis of amelanotic melanoma was made for this ocular tumour. Specific investigations for metastatic melanoma were negative.

Growth of the tumour was recorded, and the visual acuity fell to 6/36 as a result of further accumulation of subretinal fluid. A right enucleation was therefore performed. Histological examination revealed a very lightly pigmented tumour situated in a postequatorial position in the temporal region and involving the macula. Microscopic examination disclosed a small, extremely lightly pigmented, spindle-cell, choroidal malignant melanoma. The associated retinal detachment was demonstrated pathologically. There was no evidence of extrascleral extension or involvement of

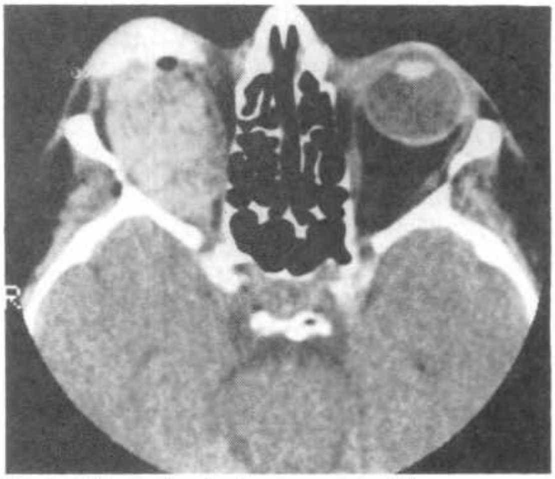

Fig. 1 *CT scan showing large recurrent soft tissue mass lying behind the prosthesis.*

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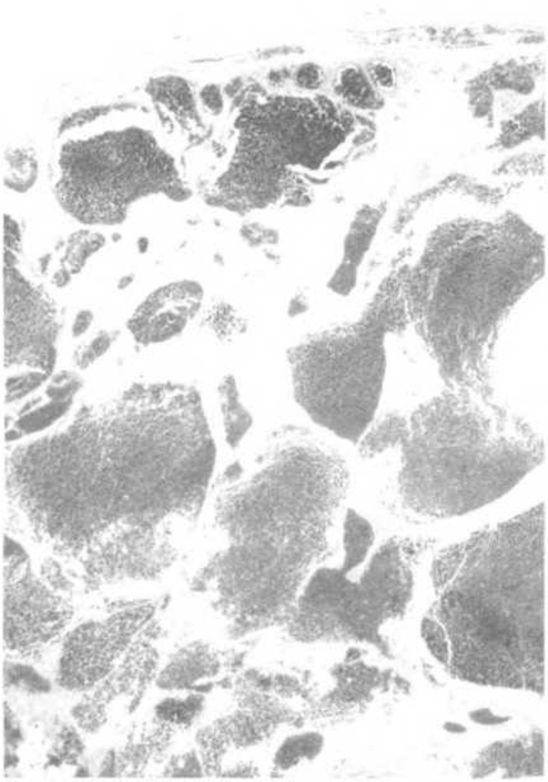

Fig. 2 *Section of orbital mass showing numerous cavernous vessels filled with blood within a thin fibrous capsule typical of a cavernous haemangioma. Haematoxylin and eosin, ×36.*

the overlying retina. Subsequently a prosthesis was fitted.

Four years later the patient reported progressive forward displacement of the prosthesis. The clinical appearance was suggestive of a massive recurrence of melanoma in the enucleated right socket. A firm, bluish black mass was seen filling the superolateral aspect of the orbit. Staging investigations including full blood count, liver function tests (including gamma GT), chest *x*-ray, liver scan, and bone scan did not show any evidence of metastatic disease. A CT head scan delineated a large mass of soft tissue density with the appearance of recurrent melanoma. (Fig. 1). There was no evidence on the scan of any extension out of the orbital cavity.

The tumour appeared well circumscribed, and it was decided to attempt excision biopsy without resorting initially to orbital exenteration. Histological examination showed an encapsulated fibrous lesion within which there were numerous thin walled, endothelium lined, blood filled spaces. The appearances were typical of a cavernous haemangioma (Fig. 2). The histology of the enucleated eye was reviewed and confirmed a spindle B cell melanoma with no special features.

Discussion

Typically, cavernous haemangioma of the orbit arises in middle life,[1-5] and it is commoner in women than in men.[6] Usually the tumour presents with a long history of moderate, unilateral, painless protrusion of the eye, though occasionally proptosis may be marked or rapidly progressive.[5] An orbital CT scan is the single most useful diagnostic test and shows a well circumscribed lesion with no osseous involvement.[5 7]

Histologically cavernous haemangioma is quite different from capillary haemangioma of the orbit,[8] and it is not considered likely that it arises by cavernous transformation of a capillary tumour present undetected from infancy.[2] Unlike capillary haemangiomas, orbital cavernous haemangiomas are discrete, well encapsulated tumours without large vascular tributaries.[9] Large and small thin walled cavernous vessels identical to those within an orbital cavernous haemangioma have been found lying outside the tumour capsule. Apparent incorporation of some of these vessels within the tumour by newly formed reactive fibrous tissue has been observed, and it has been suggested that cavernous haemangiomas arise in the orbit from enlargement of previously existing abnormal vascular channels.[9] The stimulus to this event may be disturbance in the blood flow within these vessels resulting from some extraneous event.[9]

The relevance of the present case is that no macroscopic evidence of abnormal vascular tissue within the orbit was detected during routine intraoperative inspection of the socket for evidence of extrascleral extension of uveal malignant melanoma, though a small pre-existing lesion may have been obscured by the orbital fat. The haemangioma described expanded rapidly almost to fill the orbit within four years, and this behaviour would seem to exclude steady growth of a congenital tumour as the natural history of this particular lesion. Atypical, rapid growth of cavernous haemangioma does occur but is uncommon.[5] It is tempting to speculate whether the absence of the globe in the unusual case reported here permitted rapid expansion of the tumour.

The importance of not assuming local recurrence of malignant melanoma but of obtaining further tissue for histological examination is emphasised. In this case it avoided unnecessarily radical treatment by orbital exenteration or inappropriate radiotherapy.

We thank Miss T Cocks for typing the manuscript.

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Bilateral tears of the retinal pigment epithelium

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SUMMARY This paper describes bilateral tears of the retinal pigment epithelium (RPE) which followed photocoagulation treatment of retinal pigment epithelial detachment (PED) in the right eye and which occurred spontaneously in the left eye. A 66-year-old Japanese male presented with PED approximately 4×6 disc diameters in size in his right eye, and one disc diameter in the left eye, both in the macular regions. The right PED was treated by placing a row of argon laser photocoagulation along the margin of the PED, with avoidance of the papillomacular bundle. Five days after treatment the PED enlarged peripherally beyond the coagulated site. Nineteen days later an RPE tear developed at the temporal edge of the detachment in the right eye. The remaining detached RPE retracted centrally, forming curled folds. About 40 days after the initial examination the patient complained of sudden reduction of vision in his left eye. At this time an enlargement of the PED was found in his left eye. One week after this examination a small RPE tear was found in the nasal border of the PED in the left eye. The tear in the left eye gradually developed centrally to the fovea.

Senile macular degeneration has recently become a major cause of visual loss in the elderly population.[1] Detachment of retinal pigment epithelium (PED) associated with senile macular degeneration is frequently reported.[2] Hoskin *et al.*[3] described RPE tears as a newly recognised severe complication of PEDs in senile macular degeneration. The RPE tear is reported as occurring spontaneously or after laser photocoagulation.[3-17]

There are many reports[3 8 11] on the relationship between laser photocoagulation to the PED and the pathogenesis of the RPE tears. However, the mechanism of the PRE tear has not been clarified.

In this report we describe bilateral tears of the RPE which occurred after argon laser photocoagulation to the PED in the right eye and spontaneously without any treatment in the left eye with PED.

Case report

A 66-year-old man visited our clinic on 13 December 1985 complaining of metamorphopsia in the right eye of two weeks' duration He was in good health and had no previous eye problems. His visual acuity was 0·1 (nc) in the right eye and 0·7 (1·0×+0·5 D) in the left eye. The external eye examination, pupillary responses, intraocular pressure, and results of slit-lamp examinations were normal in both eyes except for mild cataract. Pertinent findings were confined to the funduscopic examination. He had a large serous detachment of the pigment epithelium, oval in shape, which measured 4×6 disc diameters (DD) in the right macula, and a small round serous detachment of the pigment epithelium measuring 1 DD associated with drusen in the left macula. The discs and vessels were normal in both eyes. Fluorescein angiography confirmed the presence of PED and showed a delay in the overall fluorescein staining (Figs. 1A, B).

On 20 December 1985 argon laser photocoagulation was placed along the margins of the PED, with sparing of the papillomacular bundle in the right eye (44 shots with a spot size of 200 µm, a duration of 0·2 s, and a setting of 200 mW).

Five days after photocoagulation the PED enlarged in the right eye over the photocoagulation scar. Fluorescein angiography showed extensive hyperfluorescent areas along the margins of the PED. Corticosteroids were administered orally for 120 days. Nineteen days after the laser treatment a large RPE tear was demonstrated in the temporal margin of the PED, crescentic in shape, and measuring 4×0·5 DD (Fig. 2). The remaining detached RPE

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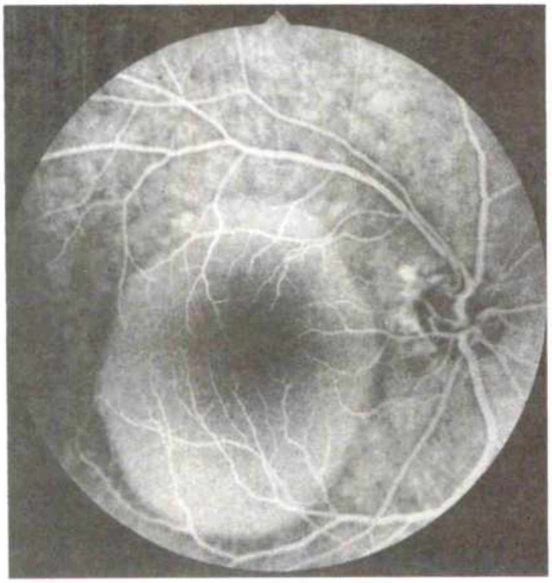

Fig. 1A

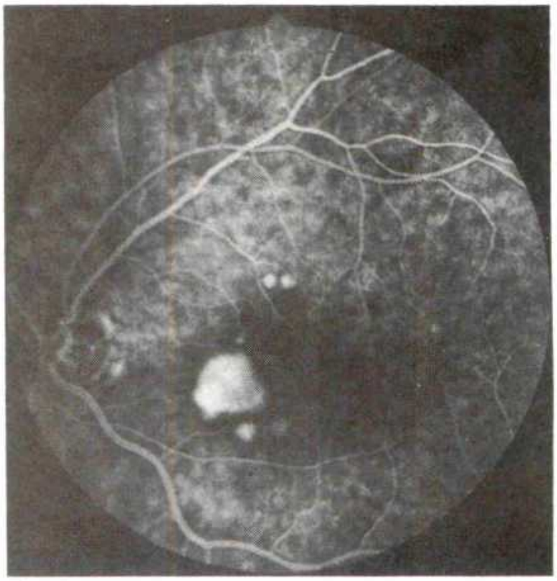

Fig. 1B

Fig. 1 A: *Fluorescein angiogram in the right eye shows large retinal pigment epithelial detachment (PED) in the macular region.* B: *Fluorescein angiogram in the left eye shows small PED associated with drusen. 13 Dec 85.*

retracted, centrally forming curled folds. Large choroidal blood vessels could be seen clearly through the tear. The free edge of the tear was not visible in the subretinal space because it retracted and infolded under the remaining elevated pigment epithelum. There was a serous detachment of the retina overlying the pigment epithelial defect.

Fluorescein angiography of 8 January 1986 gave characteristic findings. In the arterial phase hyperfluorescence of the well defined area was observed through the exposed Bruch's membrane and choroid. Within several seconds this area became intensely hyperfluorescent. The retracted area of pigment epithelium remained hypofluorescent until the late phases of the angiogram. Approximately 1 minute after the injection, dye leaked from the RPE tear into the subretinal space. There was no faint mottled fluorescein staining on the surface of the pigmented mound.

The serous retinal detachment gradually resolved.

On 22 January 1986, six weeks after his initial visit, the patient noted sudden deterioration of vision in the left eye. At that time his visual acuity was 0·04 (0·1×1·5 D) OS. Fundus examination showed a large round PED, measured 6×8 DD in the left macula.

In the PED lesion there was a small excavated zone corresponding to bare Bruch's membrane at the nasal edge of the PED. Fluorescein angiography showed a well circumscribed zone of uniform hyperfluorescein corresponding to the defect of the RPE (Fig. 3). The RPE was torn along the infranasal margin of the detachment, with retraction noted supratemporally. During the next four months the tears gradually extended to the centre of the fovea (Fig. 4). Steroid therapy was reduced gradually because the effect was not clear. On 12 September 1986, approximately nine months after the initial onset of symptom, the patient's visual acuity in the right eye had improved to 0·2 (0·6×+1·5 D), and that in the left eye to 0·3 (0·8×+1·5 D). On funduscopic examination the shape and the size of the RPE tears were unchanged except for a subretinal translucent layer of tissue within the RPE tears (Figs. 5A, B). There was no evidence of subretinal neovascularisation biomicroscopically.

Goldmann perimetry revealed normal peripheral fields with paracentral absolute scotoma which corresponded to the RPE tears in both eyes. The areas of absolute scotoma gradually became smaller and improved to become relative scotoma.

The electroretinogram (ERG) showed normal amplitudes of a and b waves in both eyes. The electro-oculogram (EOG) showed a light-peak/dark-through ratio of 1·70 on 6 February 1986 in both eyes. On 9 June 1986 it showed 1·80 in the right eye and 1·70 in the left (normal ratio >1·85).

Blood and urine examination showed no abnormality.

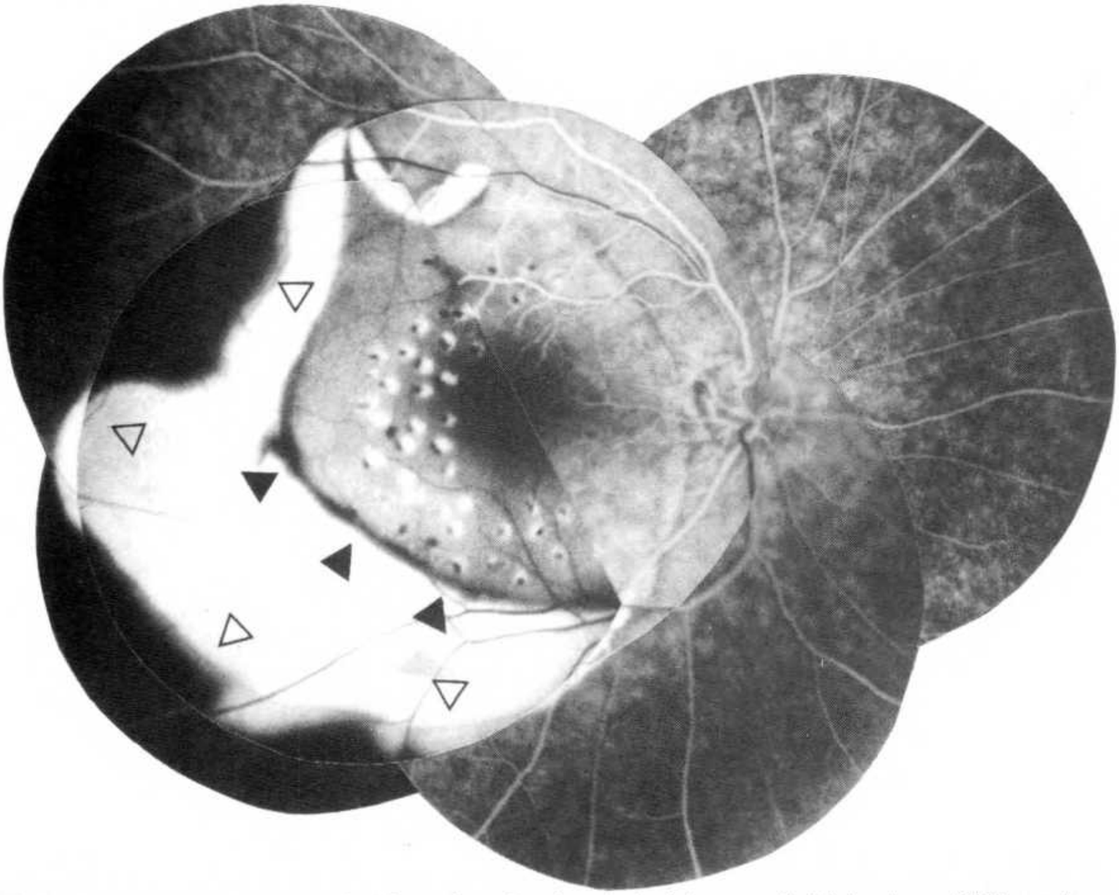

Fig. 2 *Post-treatment angiogram in the right eye shows the enlarged retinal pigment epithelial detachment (PED) over the photocoagulation scar and large tear in the retinal pigment epithelium (RPE) along inferior border of detachment (white arrows). Free edge of torn RPE is folded beneath remaining PED (black arrows), and retracted pigment epithelium remains hypofluorescent. 13 Jan 86.*

Discussion

Serous PED is a common finding in patients with senile macular degeneration.[1] Approximately 30% of the patients who have PEDs have bilateral ones.[18]

Although in the past senile macular degeneration was not so commonly found in Japan as in the USA or Europe, it has recently become one of the main diseases causing blindness. Further, there are many reports of bilateral senile macular degeneration in Japan.[19 20]

RPE tears have recently been described as a new, uncommon, but serious complication of the PED.[3-17] They occur in approximately 10% of PEDs,[5] and bilateral RPE tears have been shown to have almost similar findings and courses.[3 4 6 10] Previously they were often mistakenly diagnosed as pigment epithelial atrophy or choroidal neovascularisation.

The course of the PEDs and tears in our case was observed in detail in both eyes. Particularly in the left eye, the whole natural course of the RPE tear formation was revealed, developing first from the small PED to the large one and finally to the RPE tear. RPE tears have a characteristic clinical and angiographic appearance.[3 10] They show a flat, uniform area of exposed choroid and an area of pigment epithelial elevation. The area of denuded choroid and Bruch's membrane appears hyperfluorescent during fluorescein angiography. By contrast, the area of infolded pigment epithelium shows hypofluorescence.

Our case had characteristic fundus features. The PED in the right eye enlarged after argon laser photocoagulation, and the RPE tear occurred along the temporal margin of the enlarged PED. On the other hand a spontaneous tear was seen in the left

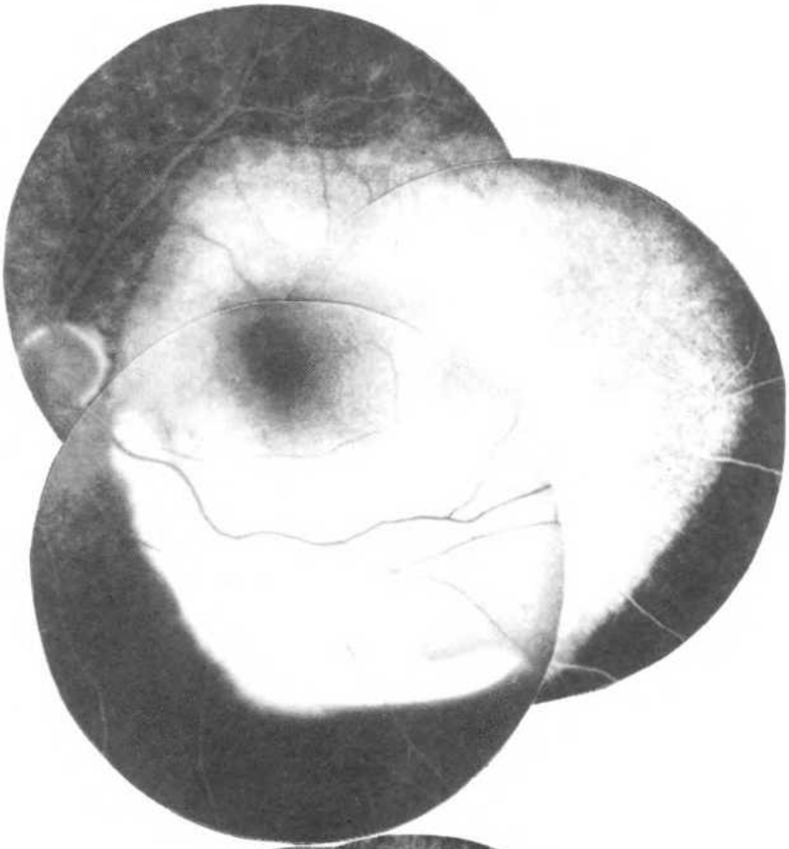

Fig. 3 *Fluorescein angiogram in the left eye shows sharply outlined margin of retinal pigment epithelial tear. 22 Jan 86.*

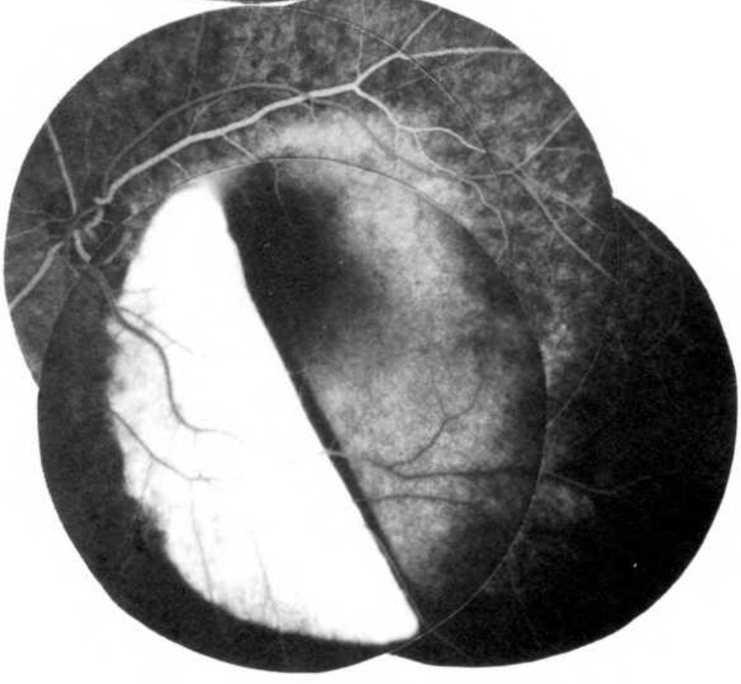

Fig. 4 *Fluorescein angiogram in the left eye shows hyperfluorescence of exposed Bruch's membrane, choroid, and folded edge of torn RPE. 20 Feb 86.*

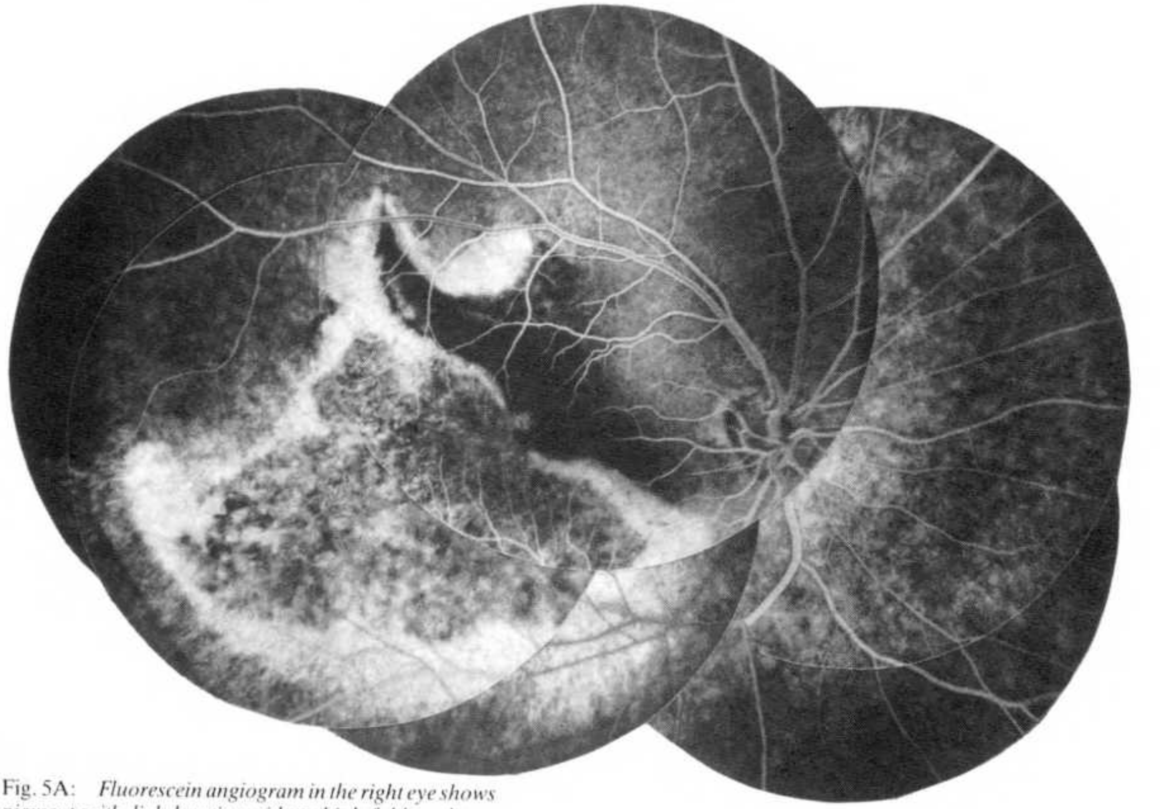

Fig. 5A: *Fluorescein angiogram in the right eye shows pigment epithelial elevation with multiple folds and tear along temporal margin. 12 Sept 86.*

eye. But the course and fundus appearance of the RPE tears were essentially similar in both eyes during the follow-up period.

Although photocoagulation has been used to flatten the PED,[11] there are many reports[8,11,12] of tearing following laser photocoagulation over the surface of the PEDs. A recent controlled study of elderly patients treated with argon laser photocoagulation[11] implied that this form of therapy confers no visual benefit and that tearing of the pigment epithelium occurs earlier in the treated eyes than in the untreated. RPE tears are the result of tractional forces acting along the margin of the PED, and the risk of tearing is greatly enhanced by laser photocoagulation.[4,8]

Our case demonstrated essentially the same evolution of the RPE tears in both eyes, though the PED of the right eye was treated with laser photocoagulation and the left was not. Argon laser photocoagulation may further weaken the RPE along the margin of the PED.[21] But in our case in spite of the laser treatment the tear in the right eye still occurred in the margins of the enlarged PED, not along the area of argon laser photocoagulation. So far as our observations go, the photocoagulation to the right eye may not be the essential factor producing the RPE tear.

Hyperfluorescent areas of leakage into the subretinal space along some margins of the PED represent an area of damaged or degenerating pigment epithelium without neovascularisation that may be more likely to tear.[6,17] These phenomena may demonstrate the importance of bending forces at the detachment margin. Krishan *et al.*[10] proposed that mechanical forces make the detachment margin the site of greatest bending stress and the most likely site for the tear.[4] The findings in our case appear to support the idea that mechanical factors have a more important role in the pathogenesis of RPE tears.[10] The tears occurred as soon as the PEDs were enlarged in both eyes. So the larger size of PEDs may also be important in the pathogenesis of the tear.[4]

The precise reasons for RPE tearing are as yet unknown. Hoskin *et al.*[3] argued from angiographic observations that separate cleavage planes may coexist, one between pigment epithelium and its basement membrane, the other between basement

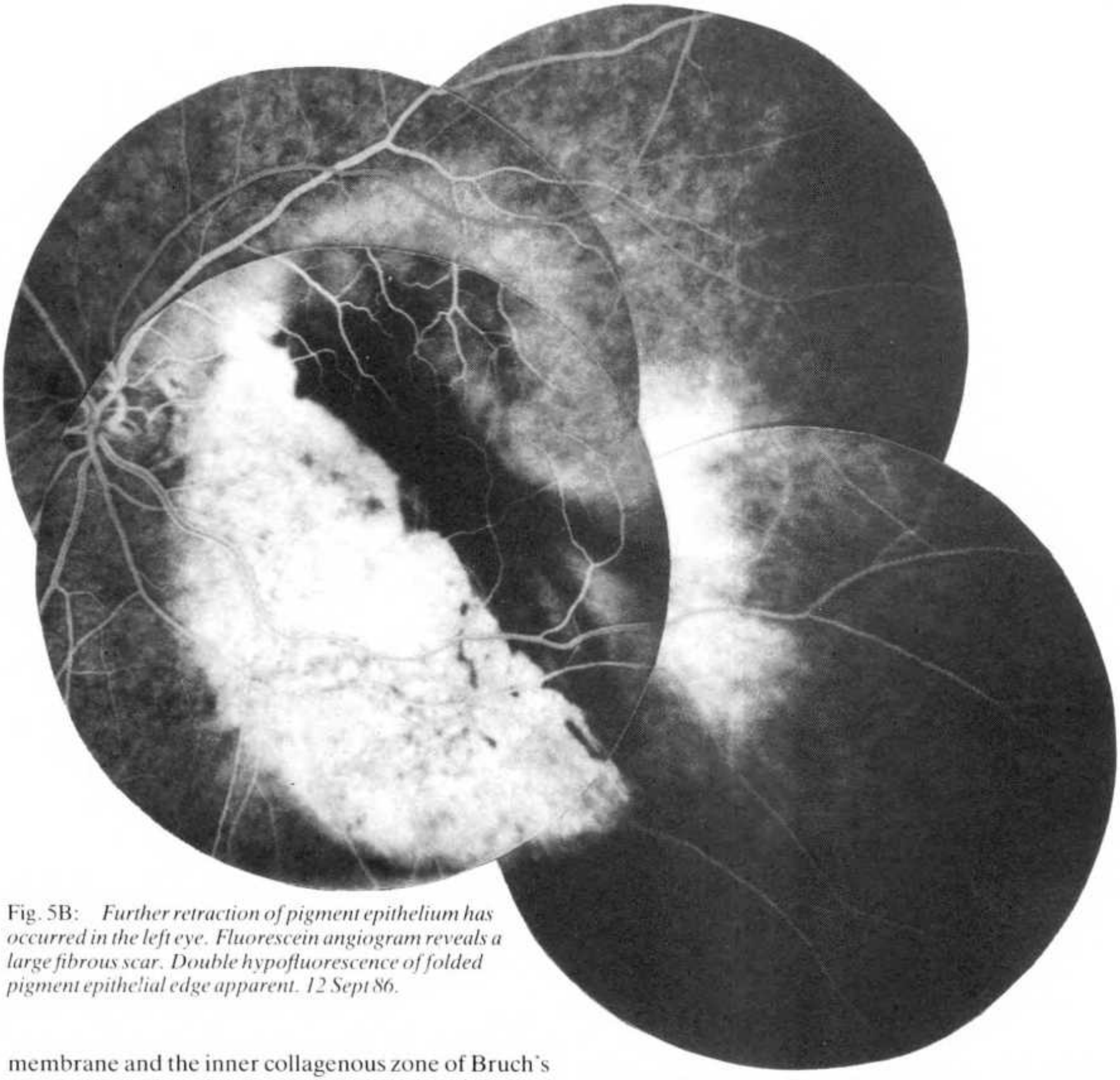

Fig. 5B: *Further retraction of pigment epithelium has occurred in the left eye. Fluorescein angiogram reveals a large fibrous scar. Double hypofluorescence of folded pigment epithelial edge apparent. 12 Sept 86.*

membrane and the inner collagenous zone of Bruch's membrane. They have suggested that RPE tears occur in the RPE that is separated from its basement membrane. They noted that the RPE in the area of the tear has a smooth, featureless appearance, and on fluorescein angiography showed uniform fluorescence, suggesting the absence of material on the under surface of the PED. Green and Yarian[9] believed that the posterior curling of the torn edge of the RPE contradicts Hoskin and colleagues' hypothesis and is further evidence that the basement membrane is adherent to the elevated torn edge of the RPE. Adjacent retinal pigment epithelial cells are joined firmly together by zonula occludentes that encircle each retinal pigment epithelial cell at its apex.[4,9] Gass[7] confirmed that the separation of the pigment epithelium from its basement membrane is not responsible for the uniform fluorescence and that its predisposing the pigment epithelium to tear is not supported by evidence from the light microscope, electron microscope, or clinical examination. Clinicopathological correlations are needed to settle this question.

The outer blood-retina barrier is disrupted because of the creation of a large defect in the pigment epithelium.[4] The dehydration of the subretinal space can no longer act in the area of the tear, and a serous retinal detachment would result. In most cases with the RPE tears, however, fluorescein leakage into the subretinal space from the area of exposed Bruch's membrane and choroid is minimal. In our case the subretinal exudate also disappeared in a few weeks. Other forces, perhaps hydrostatic in nature, may be more important in maintaining retinal aposition.[4] With time, the RPE may proliferate,[7] closing the defect and re-establishing the blood-retina barrier.[4] Once re-epithelialisation occurs, the subretinal exudate disappears.[7] Studies[13] have shown that atrophic changes occur in the choriocapillaris during the natural course of macular degeneration. These atrophic changes may be a factor in the less than expected amount of leakage that is observed in these cases.[6]

So far as we know, there are no reports on visual field changes in association with the RPE tears. In our case the absolute scotoma was observed corresponding to the RPE tear in the early stage, and it was enlarged with the development of the tear But the area of absolute scotoma became smaller, and then relative when the tear was covered with the fibrous tissue. This may suggest that the function of photoreceptors is soon recovered after RPE tears.

In the present study the ERG excluded widespread impairment of sensory retina. The EOG showed an abnormal EOG ratio, and further EOG study of the PED or the RPE tear is necessary to evaluate the RPE function.

Decker *et al.*[6] reported that 30% of PEDs developed subretinal new vessels. Subpigment epithelial choroidal neovascularisation has been suggested the primary cause of the detachment and tear in the pigment epithelium.[7] The present case showed neither choroidal neovascularisation nor subretinal or subpigmentary epithelial haemorrhage.

There is no treatment of confirmed value for RPE tears, but there is a report[14] stating that photocoagulation is recommended for their early treatment when they are associated with serous sensory retinal detachment.

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Infectious crystalline keratopathy

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SUMMARY We present a patient who developed a crystalline keratopathy after a penetrating keratoplasty. This rare complication can be caused by bacterial infection, and the patient responded to the appropriate antibiotic therapy. The literature is reviewed and possible causes and mechanisms of the crystalline appearance are discussed.

A crystalline appearance within the stroma of the cornea may be caused by a variety of conditions including lipid and metabolic disorders such as cystinosis and monoclonal gammopathy in association with multiple myeloma. More unexpectedly it can occur as a complication of penetrating keratoplasty following either infection[1-5] or rejection.[6 7] We report here on a patient who developed a crystalline keratopathy following a graft. The cause of the keratopathy was considered to be infective and the condition resolved on antibacterial treatment.

Case reports

A 32-year-old man with advanced keratoconus underwent an uneventful penetrating keratoplasty in December 1984. A whole donor eye was used, and the graft was sutured in place with a continuous 10/0 nylon suture. The surgery was uncomplicated though technically difficult because of thinning of the host cornea peripherally. Six days later there was an aequeous leak, with hypotony. The anterior chamber was shallow, the suture loose, and the graft oedematous. Following placement of a single 10/0 nylon suture at the site of the leak the anterior chamber reformed and the leak was sealed; the cornea cleared, and there were no synechiae. Fifteen days later the continuous suture had loosened slightly between 8 and 10 o'clock at the site of the leak, and mucus had become adherent to it. This caused no problems, and no change in management was required save for the addition of 10% acetylcystine drops four times daily.

Ten months after surgery, in October 1985, the suture had loosened superiorly, and this section was removed. At this stage the corrected visual acuity was 6/5, and the patient was taking prednisolone (Predsol) twice daily in addition to the acetylcystine. A few days after the removal of the suture the graft developed a superficial corneal crystalline stromal infiltrate (Fig. 1) at 9 o'clock, which appeared to be associated with a suture track. The epithelium was intact and the remainder of the graft clear; the anterior chamber contained occasional cells. Conjunctival swabs were taken, but no bacteria grew on blood agar plates. A corneal scraping was not carried out because of the intact epithelium.

Treatment with prednisolone was continued and intensive topical gentamicin and methicillin started. After five days, when the possibility of a streptoccocal infection was realised in the light of the experience of others,[1-5] treatment was changed to topical penicillin and corticosteroids. The lesion

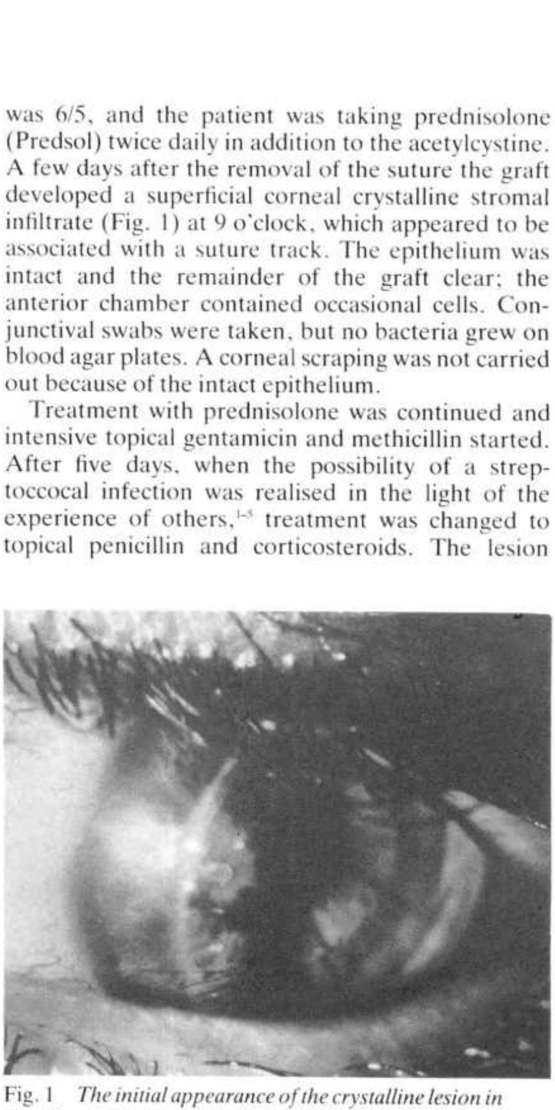

Fig. 1 *The initial appearance of the crystalline lesion in October 1985.*

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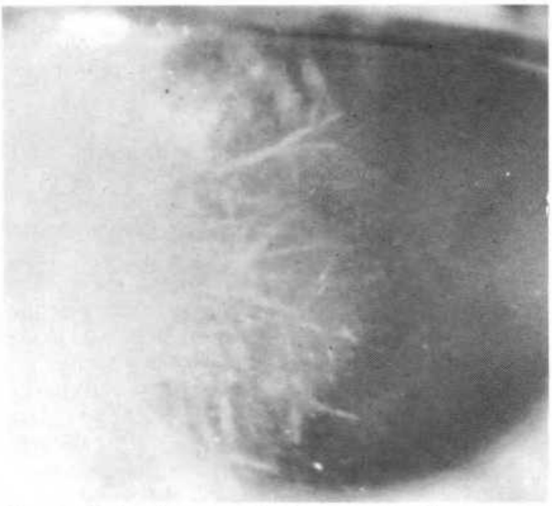

Fig. 2 *The development of further crystalline deposits in February 1986.*

regressed. After six weeks, in November 1985, the antibiotics were stopped.

In February 1986, three months after withdrawal of the antibiotics, the stromal lesion recurred and was associated with a crystalline opacity spreading into the graft at midstromal level. Topical penicillin and steroid was again started. A corneal scrape failed to grow any organisms when directly plated on to blood agar; a Gram stain was not performed. The eye initially worsened. It became painful, with the development of photophobia and redness, but the clinical signs were unchanged (Figs. 2, 3). Penicillin was stopped, and, because of the possibility of a more serious infection, the patient was given a subconjunctival injection of gentamicin and methicillin and was started on systemic treatment with the same antibiotics. The eye improved on this regimen, with a reduction in the area of opacification and no progression of the crystalline keratopathy. Two weeks after the acute episode the patient was using gentamicin and methicillin every two hours and prednisolone three times daily. The gentamicin was stopped one week later.

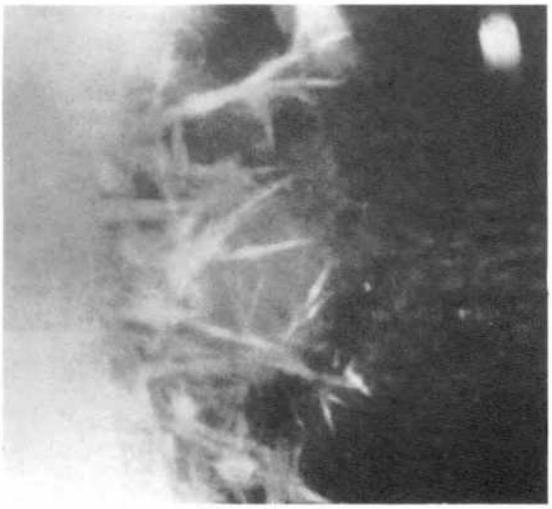

Fig. 3 *Magnified view of the crystalline deposits in February 1986.*

Three months later the crystals had markedly regressed. The patient at this time was taking prednisolone and methicillin twice daily, having received antibiotics for a total of three months. At follow-up in September 1986 there had been no recurrence, and the corrected visual acuity was 6/9. Slight stromal scarring persisted peripherally at 9 o'clock, but all crystalline appearances had regressed completely. Subsequent follow-up revealed no change (Fig. 4).

Discussion

Gorovoy *et al.*[3] reported the first case of a crystal-like deposition associated with infection in a corneal graft. In his case, as in other reports, there was no sign of ocular inflammation. The crystalline appearance progressed over five months, and the patient eventually required a regraft. There is no mention of any culture being performed, and no antibacterial therapy was given. Analysis of the corneal button removed showed a localised ingrowth of epithelium associated with a suture, and from this area colonies of Gram-positive bacteria were seen extending between the stromal lamellae.

Meisler *et al.*[1] presented an initial series of three

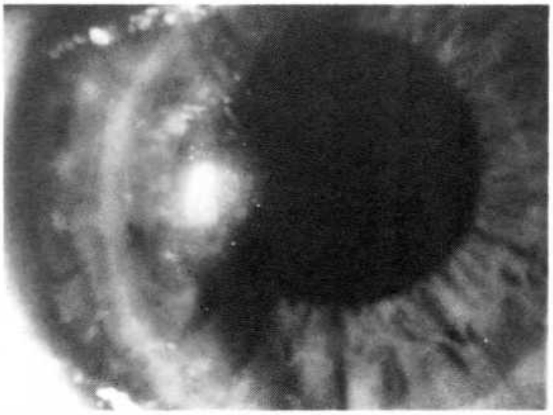

Fig. 4 *The corneal appearance in February 1987. Note that central white area is light reflection.*

patients with infectious crystalline keratopathy: two developed after penetrating keratoplasty, one in a herpetic eye. Two of the three patients grew an α-haemolytic streptococcus either from a corneal scrape or from a diagnostic keratectomy. All three of his patients were treated with antibiotics. The lesions resolved, leaving a variable amount of scarring or corneal oedema.

Samples *et al.*[2] reported on a patient, again showing no sign of ocular inflammation, who was treated for a presumed fungal infection. Diagnostic keratectomy had failed to demonstrate any organisms. The situation worsened so that a further graft had to be performed. Examination of the corneal button showed dense bacterial colonies beneath Bowman's membrane.

Reiss[5] reported on a patient in whom *Streptococcus viridans* had been cultured from a corneal scrape. A repeated graft had to be performed, however, and microscopy of the button again demonstrated the presence of intrastromal bacteria.

The case reported in this paper follows a similar pattern to those reviewed above. The recurrence of the lesion after a short course of antibiotics indicates that topical treatment must be continued for some months to eradicate the infection. The location of the organism within the stroma, demonstrated by electron microscopy[1-3,5] not only makes it difficult to obtain specimens to culture an organism but also presumably lends protection to the bacteria from the effect of topically applied antibiotic

The way in which the bacteria penetrate the corneal stroma and the reason for their growth in the anterior part of the stroma is open to speculation. A suture track would seem the most probable mode of bacterial entry into the stroma, but any break in Bowman's membrane, no matter how caused, would suffice. The immunosuppressive effect of topical corticosteroids may also play a part. All but one of the cases reported have occurred in patients with corneal grafts, for whom prolonged steroid treatment is usually required. There have been no reports of a similar process occurring in cataract surgery, where the period of steroid treatment is much shorter. Samples *et al.*[2] suggested that the predilection of the organism for the anterior stroma reflects an advantageous environment for growth at this depth in the cornea.

The nature of the crystalline appearance itself is also obscure. Reiss *et al.*[5] suggested that it may be formed by the bacterial colonies themselves as they grow between the lamellae of the corneal stroma. With the electron microscope Samples *et al.*[2] observed electron dense bodies with needle-like projections and considered that they were responsible for the crystalline appearance. The origin of these bodies was uncertain.

It might be suggested that the crystals are the result of the precipitation of immune complexes formed as a result of an immunological response to intrastromal bacteria. This would be akin to the suggested aetiology of the crystals seen in graft rejection.[6,7] These have been reported as appearing at the deep stromal level between five and 30 days after rejection of the graft. The crystals differ from those seen in the case of infectious crystalline keratopathy in that they are found in the deep stroma and respond to steroid treatment alone. The suggested cause of these crystals is a precipitation of immune complexes formed between host antibody and donor stromal antigens A further suggestion had been that the crystals may be the result of lipid deposition.[2] The appearance is not, however, typical of that seen in lipid keratopathy and it would not be expected to resolve with antibiotic treatment.

CONCLUSION

Stromal infection of a corneal graft may present as a superficial or midstromal crystalline keratopathy in a quiet or minimally inflamed eye. It is associated with the presence of intrastromal bacteria and must be differentiated from the deep crystalline keratopathy seen in graft rejection. Treatment should be with thorough, prolonged application of antibiotics, which is curative.

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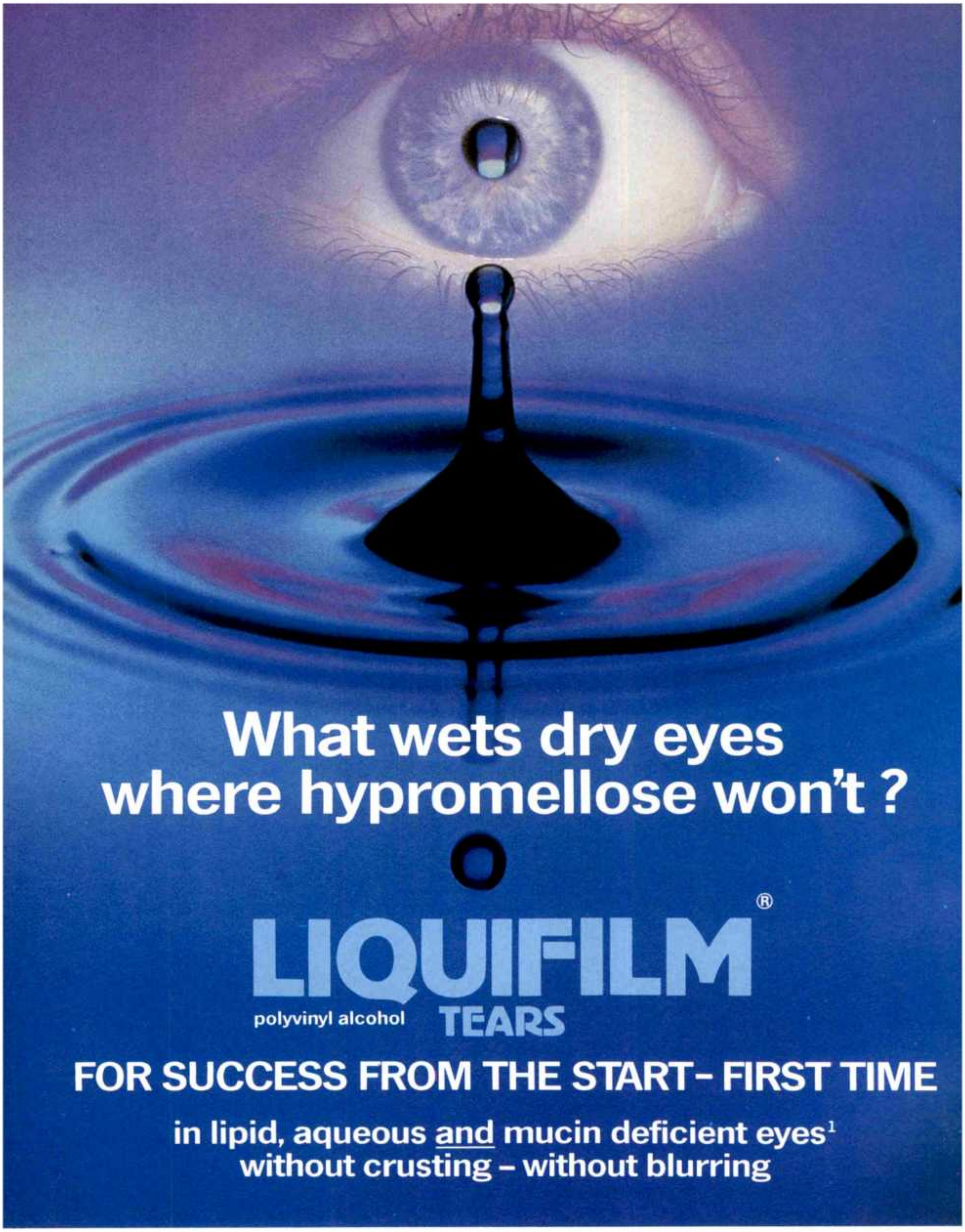
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British Journal of Ophthalmology, 1988, 72, 631–633

Globe luxation in histiocytosis X

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SUMMARY A boy with histiocytosis X, first diagnosed at the age of 9 months, presented at the age of 5 years with left globe luxation. Under general anaesthesia the globe was reduced and a temporary paracentral tarsorrhaphy carried out. He was started on a course of oral steroids. Two years later he had normal visual acuity, full ocular movements, and healthy fundi.

Histiocytosis X, Langerhans cell histiocytosis, is an uncommon condition in which non-malignant histiocytes proliferate and invade various organs including skin, bone, liver, spleen, lung, and bone marrow. In most cases in children the condition is self-limiting, though a few have progressive disease and die from failure of infiltrated organs.[1 2] Orbital involvement occurs in 20–25% of patients with histiocytosis X, and proptosis is the main ophthalmic problem.[3-5]

Globe luxation is rare, generally being precipitated by raised intraorbital pressure,[6] lid manipulation,[7 8] or trauma[9] in patients with shallow orbits,[10 11] lax orbital ligaments,[12] or anomalous extraocular muscles.[13] Expanding orbital tumours may produce marked proptosis, but actual globe luxation is exceedingly rare. We describe a 5-year-old boy with orbital involvement by histiocytosis X who developed a luxated left globe

Case history

At the age of 9 months this boy was diagnosed as having histiocytosis X when he presented with a cystic swelling behind his left ear, a follicular maculopapular rash, hepatosplenomegaly, miliary shadowing on chest *x*-ray, and a skull *x*-ray with multiple osteolytic lesions. Biopsy of both skin and the mass behind his left ear confirmed the diagnosis of histiocytosis X. Treatment was started with vinblastine, oral prednisone, and cyclophosphamide. On this regimen the histiocytosis X resolved, but over the subsequent three and a half years he had three further relapses involving the skin, left mastoid, and occipital region and was treated with courses of vinblastine and prednisone and irradiation to the mastoid.

At the age of 3 he developed bilateral proptosis, more marked on the left. Investigations again revealed multiple bony lucencies in the skull. His proptosis was resistant to vinblastine and prednisone, and VP16 produced only minimal improvement. He therefore received radiotherapy (100 cGy) to both orbits at the age of 3 years 11 months. The proptosis did not completely respond, and at the age of 5 he was again put on prednisone 20 mg daily, and because of left lagophthalmos a lateral tarsorrhaphy was carried out. This produced a slow response, and the steroid dosage was reduced to 10 mg of prednisone on alternate days. A CT scan of his skull showed persistent bony defects of the middle cranial fossa, especially the lesser wing of the sphenoid bone and the petrous temporal bone.

At the age of 5 years 3 months he presented as an emergency with left globe luxation, which occurred while he was straining and which would not spontaneously reduce. His left visual acuity was counting fingers only, he had a hazy left cornea, and, while there was no definite afferent pupil defect, the left pupil showed a very sluggish reaction to light A CT scan showed a much enlarged retroorbital mass (Fig. 1). Under an anaesthetic the luxated globe was reduced, a paracentral tarsorrhaphy performed, and the dose of prednisone increased to 60 mg daily. This produced a substantial reduction in the proptosis, and after three weeks the tarsorrhaphy was opened. During the subsequent 10 months the dose of steroids was gradually reduced to 15 mg on alternate days. Two years later the left eye shows no evidence of any permanent damage due to the luxation (Fig 2). He had a visual acuity of 6/6 in both eyes, a full range of ocular movements, and healthy optic discs and fundi.

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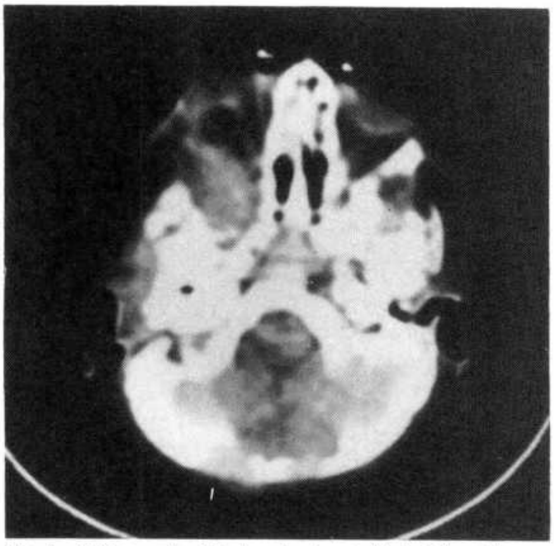

Fig. 1 *CT scan of orbits showing luxated left globe with a large retroorbital mass.*

Visual evoked responses to a pattern reversal stimulus with a 50-minute check at 95% and 50% were entirely within normal limits with respect to both latency and amplitude from each eye.

There have been no further episodes of globe luxation.

Discussion

Orbital involvement in histiocytosis X usually occurs in the chronic multisystem form of the condition which was previously called Hand-Schüller-Christian disease and rarely presents in the acute multisystem variety of Letterer-Siwe disease.[3 4] In one series with only soft tissue involvement the orbits were not affected, suggesting that they become so from adjacent bony involvement.[5] The commonest signs of ophthalmic involvement are bilateral or unilateral proptosis and less frequently papilloedema with optic atrophy.[3-5] When bilateral papilloedema is present it is often associated with central nervous system disease, and it may result in bilateral optic atrophy with visual impairment.[3] Globe luxation is not described in several reviews of histiocytosis X.[3-5]

In most cases of globe luxation due to either a shallow orbit or lax orbital ligaments reduction is easily achieved, and the patients have a good visual prognosis.[14] In contrast luxation due to space occupying lesions is much more likely to cause loss of vision, and the management of the patient often involves orbital decompression,[15] tumour excision, and very occasionally enucleation.[16]

As the majority of lesions in histiocytosis X are self-limiting, conservative treatment without jeopardising vision should be attempted. In the present case simple reduction supported by a temporary tarsorrhaphy and oral steroids produced a very satisfactory long-term result. The pre-existing lateral tarsorrhaphy which had been carried out to prevent exposure keratitis may have produced a tighter orbit, which would increase intraorbital pressure and increase the risk of luxation. Further, once the luxation had occurred, the smaller than normal palpebral aperture would have hindered reduction of the globe.

Radiotherapy,[17] excision of the tumour mass, orbital decompression, or intralesional steroids are alternative approaches. Radiotherapy had already been administered in this case, and the other methods were not only more invasive than that adopted but also more likely to have an adverse effect on vision and ocular motility.[18 19]

Severe proptosis in histiocytosis X should be carefully observed, and, if symptoms are progressive, therapy should be directed to preventing globe luxation. If this does occur, then conservative management may produce the best long-term visual prognosis. Lateral tarsorrhaphy should be avoided, for although it relieves corneal exposure it may increase the long-term risk of globe luxation.

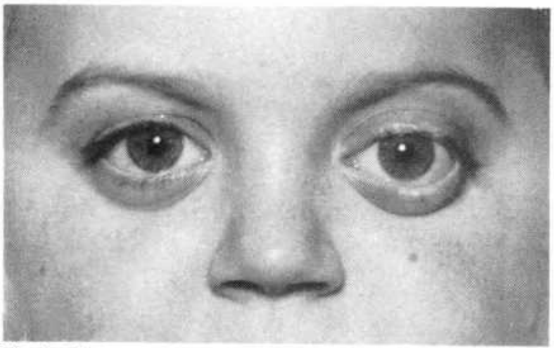

Fig. 2 *Patient at 2½ years and after globe luxation.*

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Floppy eyelid syndrome associated with keratotorus

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SUMMARY A case of floppy eyelid syndrome associated with keratotorus is presented. The patient was thoroughly examined and followed up for several years. During that time he developed an acute corneal hydrops. The importance of this association for the better understanding of the syndrome is discussed.

The floppy eyelid syndrome is a fairly newly recognised clinical entity of so far unknown aetiology. The first authors to describe it[1 2] noted the association of the syndrome with other ocular or systemic disorders. We report here on a patient who has had floppy eyelids associated with a specific corneal ectasia—keratotorus.

Case report

A 54-year-old man was seen for the first time at the University Eye Clinic in 1961. Stanković and Stanković published a detailed description of this case.[3] He had a typical bilateral keratotorus with myopic astigmatism against the rule and clear pyriform ectatic cornea. No changes in the lids were recorded.

In 1985 he presented to us with a red, inflamed right eye together with acute oedema of the ectatic part of the cornea. The cornea of the left eye was clear, with typical unchanged keratotorus. There was a punctate keratopathy of the entire corneal surface in both eyes. The upper eye lids could be easily everted and pulled up. The palpebral conjunctiva of the upper lid, especially in the right eye, showed a

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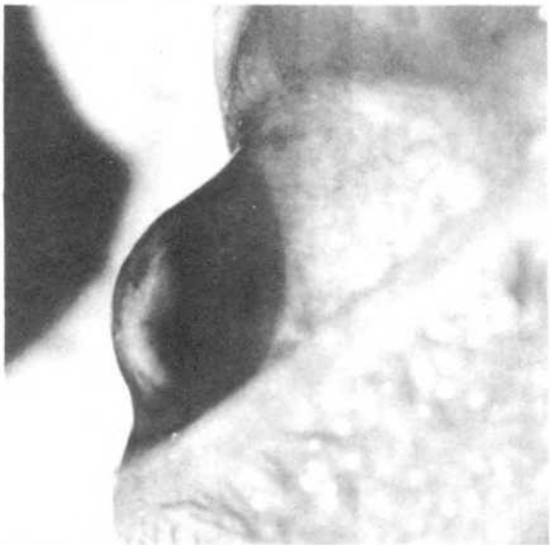

Fig. 1 *Acute keratotorus with everted floppy eyelid.*

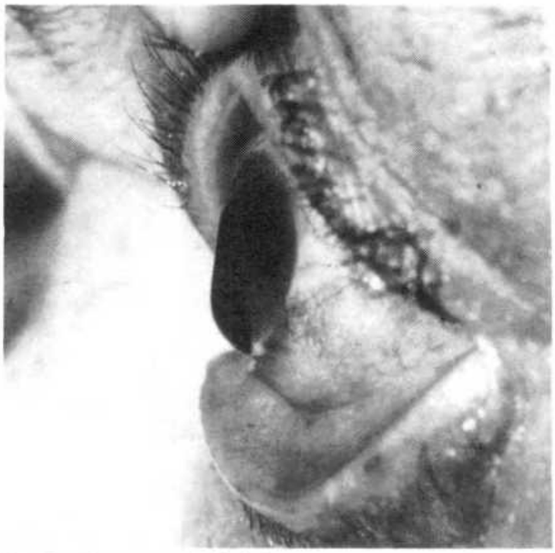

Fig. 2 *Keratotorus in the left eye.*

marked papillary hypertrophy. The patient was not obese

Local corticosteroids were administered, and after two weeks the corneal oedema as well as the inflammatory reaction almost disappeared.

In the next few months the eye was quiet and the corneal oedema resolved, but the scar in the central ectatic part continued to show a typical pyriform ectasia. The patient refused any type of surgery.

Discussion

The first recognised association of the floppy eyelid syndrome was with obesity and nocturnal lagophthalmos,[1,2] later with hyperglycinaemia,[4] blepharochalasis,[5] and tapetoretinal degeneration.[6] There has been only one report on the association of floppy eyelid with keratoconus[6] but not a single one with keratotorus, or acute hydrops of the cornea. It is true, however, that there is no unanimity of opinion on the relation of keratoconus and keratotorus with pellucidal marginal degeneration. Most European ophthalmologists[3,7,8] regard them as distinct clinical entities, but some American authors consider clinically different corneal protrusions to be variants of one and the same condition.[9] Whichever is correct, the floppy eyelid syndrome in our patient was associated with acute hydrops of an unusually ectatic cornea (keratotorus).

There are two theories about the possible aetiology of the floppy eyelid syndrome. It is either the result of a partial nocturnal lagophthalmos or an ocular manifestation of a so far unknown systemic disorder. The case we describe here seems to support the latter theory. We have already seen a patient with both keratoconus and floppy eyelids, and similar observations have been reported.[6] However, there has always been plenty of evidence of the association of keratoconus with many systemic diseases, to mention only Down's syndrome endocrine disorders, and atopic disease.

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α_1-Antitrypsin phenotypes in acute anterior uveitis

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SUMMARY The α_1-antitrypsin phenotype PiMZ has been reported to have a higher than normal incidence in patients with acute anterior uveitis, indicating an important role in the immunogenetics of this condition. We have determined the incidence of this phenotype in 72 patients with acute anterior uveitis. It was found to occur in four patients (5·6% of the total), with the highest incidence (3/34 or 8·8%, $p<0.001$) in patients negative for HLA B27 and without sacroiliac joint disease. The incidence in HLA B27 positive patients was normal. No correlation was found with the severity, bilaterality, or recurrence of uveitis. Although this increased incidence is statistically significant in comparison with the normal population incidence of 2·6%, its direct clinical significance is questionable; the most likely explanation for it includes possible linkage with other immunoregulatory genes. We also found a lower than expected incidence of the phenotype PiMS, and discuss the relevance of this finding.

The association between HLA B27, ankylosing spondylitis (AS), and acute anterior uveitis (AAU) has been known for over 14 years.[1] This tissue type, which is found in 7 to 8% of the general population, occurs in virtually all patients with both anterior uveitis and ankylosing spondylitis but only 45 to 50% of patients who have anterior uveitis without systemic disease.[2,3] Furthermore, only 0·15% of the HLA B27 positive population will ever get anterior uveitis. It is therefore apparent that there must be some alternative genetic or environmental factor which predisposes an individual to attacks of acute anterior uveitis.

In 1978 Brewerton *et al.*[4] demonstrated a substantially increased incidence of the α_1-antitrypsin phenotype PiMZ (associated with relatively lower blood levels of this major protease inhibiting enzyme) in patients with anterior uveitis, occurring in 30% of those with anterior uveitis and ankylosing spondylitis and 21% of those with anterior uveitis alone. The α_1-antitrypsin phenotypes are internationally annotated by an alphabetical method, prefixed by Pi (protease inhibitor), with one letter for each allele (some of which have several subtypes, annotated numerically) Some 59 different alleles have been recognised, the most prevalent being M (hence PiMM is the most common phenotype). As the Pi gene locus is on chromosome 14 while that of the HLA system is on 6, this suggested a hitherto unrecognised inherited susceptibility to anterior uveitis capable of operating independently of HLA B27 through insufficient inhibition of inflammatory proteolysis by α_1-antitrypsin.

Although these findings have been confirmed by some authors,[5,6] albeit with lower incidences, they have been refuted by others.[7,8] The result is a lack of a definitive understanding of whether a deficiency of α_1-antitrypsin is of clinical importance in the susceptibility of an individual to anterior uveitis. We now present our data from a well-defined group of 72 patients with acute anterior uveitis who presented to St Thomas's Hospital, London, between 1984 and 1986, and who were classified according to race, HLA B27 status, sacroiliac joint disease, recurrence, bilaterality, and severity of inflammation.

Subjects and methods

In this study acute anterior uveitis is defined as an acute, non-granulomatous inflammation of the

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anterior uveal tract. It was usually unilateral, and characterised by a history of pain, photophobia, and blurring of vision, with circumcorneal injection, keratic precipitates, and cells and flare in the anterior chamber

The 72 patients who presented to the Eye Casualty Department with anterior uveitis were studied in our uveitis clinic, where we recorded their age (range 16 to 73 years, mean 43), sex (41 male, 31 female), and race. Other details included whether it was a first or recurrent attack of AAU and whether it was unilateral or bilateral. The severity of inflammation at presentation was clinically graded as mild, moderate, or severe In those patients seen when convalescent these details were obtained from the records.

Tissue typing, in order to ascertain HLA B27 status, was carried out on a 20 ml sample of citrated venous blood.

α_1-Antitrypsin phenotyping was performed at the Protein Reference Unit of the Royal Hallamshire Hospital, Sheffield, by the established technique of isoelectric focusing of serum samples on polyacrylamide gels, in accordance with Brewerton's study[4] Incidence values for the normal south-east England population were used as controls in this study.[9]

Radiological assessment of the patients' sacroiliac joints was carried out according to New York criteria[10] by a member of the Department of Radiology, St Thomas's Hospital, who was not informed of their HLA B27 status or any relevant history other than the fact that all had anterior uveitis. Patients scoring 2 or more out of 4 by this method were classified as having sacroiliac joint disease.

The results were analysed by χ^2 tests.

Results

The incidences of the major phenotypes in our study group are displayed in Table 1, which also shows the results divided into different ethnic groups. The normal values for the United Kingdom are given as controls. As can be seen, the study population as a whole was an atypical sample ($p<0{\cdot}05$) owing to a possibly higher incidence of phenotype PiMZ (5·6%, $p=0{\cdot}10$) and a slightly lower incidence of PiMS (2·8%, $0{\cdot}05<p<0{\cdot}10$). When the group was subdivided according to ethnic origin, only the Caucasian group ($n=56$) was large enough to warrant valid statistical analysis, and the results of this group mirrored those of the study group as a whole, with a PiMZ incidence of 3/56 (5·4%) and a PiMS incidence of 2/56 (3·6%).

Table 1 *Incidences of the major Pi phenotypes found in our study group compared with those of the UK population as controls (percentage in parentheses)*

Phenotypes	*n*	*PiMM*	*PiMS*	*PiMZ*	*PiFM**
UK incidence		(86·5)	(9·3)	(2·6)	(0·7)
Study group	72	65 (90·3)	2 (2·8)	4 (5·6)	1 (1·4)
Caucasian	56	50 (89·3)	2 (3·6)	3 (5·4)	1 (1·8)
Negro	7	7 (100)	–	–	–
Asian	5	4 (80)	–	1 (20)	–
Oriental	4	4 (100)	–	–	–

*No known clinical significance

Table 2 *Phenotype incidences in HLA B27 positive and negative patients, and in those with and without evidence of sacroiliac joint (SIJ) involvement (percentages in parentheses)*

Phenotypes	*n*	*PiMM*	*PiMS*	*PiMZ*	*PiIM*
B27 negative	34	30 (88·2)	–	3 (8·8)	1 (2·9)
B27 positive	38	35 (92·1)	2 (5·3)	1 (2·6)	–
SIJ neg*	57	53 (93·0)	–	3 (5·3)	1 (1·8)
SIJ pos†	15	12 (80·0)	2 (13·3)	1 (6·7)	–
B27 positive, SIJ neg	23	23 (100)	–	–	–

*Twenty three HLA B27 positive and 34 negative
†All HLA B27 positive

When the patients were divided into those who were HLA B27 positive and negative, and those who did and did not have radiological evidence of sacroiliac involvement (Table 2), it was found that our sample population showed a typical distribution of the incidences of HLA B27 (38/72, 52·8%) and sacroiliac disease (15/72, 20·8%) for patients with anterior uveitis ($p>0{\cdot}50$). Analysis of the individual groups showed that the B27 negative patients followed the trend of a possibly lower incidence of PiMS ($0{\cdot}05<p<0{\cdot}10$) and a higher incidence of PiMZ ($p<0{\cdot}025$) when compared with the normal United Kingdom population. When the B27 positive group was considered as a whole, it showed a normal distribution of phenotypes ($p>0{\cdot}75$), with no significant difference between those who had evidence of sacroiliac disease and those who did not Those patients who had no sacroiliac involvement (irrespective of HLA B27 status), like the B27 negative group, also showed a lower incidence of PiMS ($p<0{\cdot}025$) and a possibly higher incidence of PiMZ ($0{\cdot}05<p<0{\cdot}10$). Those who did have sacroiliac involvement (all HLA B27 positive) had an essentially normal distribution of phenotypes ($p>0{\cdot}75$)

Our results showed no significant difference in the phenotype incidences when the severity of anterior uveitis was expressed in terms of bilateral or recurrent disease (Table 3). Only seven of the 72 patients had bilateral disease, and all were PiMM, the remaining 63 (laterality not recorded in two patients) having the same phenotype incidences as the whole group. There was no significant difference between those who had recurrent inflammation and those presenting for the first time, nor between those presenting with clinically mild, moderate, or severe inflammation.

Table 3 *Phenotype incidences in bilateral and recurrent, and mild, moderate, and severe acute anterior uveitis (percentages in parentheses)*

Phenotypes	*n*	*PiMM*	*PiMS*	*PiMZ*	*PiFM*
Unilateral	63	56 (88·8)	2 (3 2)	4 (6·3)	1 (1 6)
Bilateral	7	7 (100)	–	–	–
Not recorded	2	2 (100)	–	–	–
First attack	37	33 (89 2)	1 (2·7)	2 (5·4)	1 (2 7)
Recurrent	33	30 (90·9)	1 (3 0)	2 (6·1)	–
Not recorded	2	2 (100)	–	–	–
Mild	21	20 (95 2)	–	1 (4·8)	–
Moderate	39	34 (87 2)	2 (5·1)	2 (5 1)	1 (2·6)
Severe	12	11 (91·7)	–	1 (8·3)	–

Of the four patients with the PiMZ phenotype only one was HLA B27 positive, and she presented as a severe, recurrent, uniocular inflammation with grade 2 radiological evidence of sacroiliac disease. The remaining three were all B27 negative, with no evidence of sacroiliac involvement. Two presented with moderate inflammation (one of whom had recurrent anterior uveitis), and one had a mild first attack. All three were unilateral.

Discussion

There are at least 59 different alleles for the α_1-antitrypsin gene, only two of which, Z and (to a lesser extent) S, are associated with a deficiency of the enzyme. Severe deficiency produced by homozygote PiZZ or PiSS, and associated with primary emphysema and juvenile cirrhosis, is well documented.[11] Heterozygote phenotypes for Z and S, occurring with M or 0 (null), have been suggested to be associated with less severe hepatic and pulmonary disease, juvenile arthritis,[12] and psoriasis,[13] as well as anterior uveitis

Table 4 *Comparisons of our results with the PiMZ incidences in other studies of acute anterior uveitis, with and without sacroiliac joint (SIJ) disease (percentages in parentheses)*

Study group	*SIJ disease negative*	*SIJ disease positive*
Fearnley *et al*	3/37 (5 3)	1/15 (6 7)
Brewerton *et al.*[4]	10/47 (21 3)	10/33 (30 3)
(later reappraised)	9/64 (14·1)	15/52 (28 8)
LeClerq *et al.*[6]	4/30 (13 3)	4/29 (13·8)
Wakefield *et al*[5]	3/80 (3 8)	
Grabner *et al*[8]	3/65 (4 6)	
Brown *et al*[7]	0/133 (0)	

An increased incidence of phenotype PiMZ was seen in our patients when taken as a whole, with values ranging up to 8·8% depending on which subgroup is considered. In none of these cases, however, does it occur with the frequency described by some workers (Table 4). Although our results are just statistically significant when compared with the normal south-east England incidence of 2·6%,[9] it is difficult to argue their clinical significance in proving that the relatively lower levels of α_1-antitrypsin associated with phenotype PiMZ do predispose to anterior uveitis. This argument is further confounded by the fact that uveitis is not a major clinical feature in those who have the PiZZ genotype.[11]

Those authors whose results failed to show any significant difference in the incidence of phenotype PiMZ in anterior uveitis[7 8] have suggested that this might be due to differences in the ethnic make-up of the various sample populations. It is known that the incidence of PiMZ can vary between 1 and 4% for different populations (it occurs much less frequently in Negroes and Asians), but this is not enough to explain the magnitude of the discrepancies seen between different study groups (Table 4). Our population came from the same area as that of Brewerton *et al*,[4] in London, and, although it is moderately heterogeneous, one would expect a closer correlation between our results. Instead we found almost the opposite, with no particular correlation between the incidence of PiMZ and sacroiliac joint involvement (all HLA B27 positive), as one might expect if the Pi system was independent of the HLA system. Brewerton himself thought that such differences seen might be due to the more rigorous selection techniques used in his studies,[14] but we have used similarly rigorous selection techniques ourselves with our study group. Indeed, by using only radiological criteria to assess sacroiliac disease, we have probably created several false negatives (patients who have early sacroiliac involvement but have not yet developed radiological evidence of it), which would serve only to enhance the incidence reported in those patients who were diagnosed as having sacroiliac disease. Not only did we fail to demonstrate such a high incidence of PiMZ in anterior uveitis, but we also found no significant difference in its incidence between those uveitic patients who also had sacroiliac joint disease and those who did not.[4 14] In fact, the incidence of PiMZ in our study group was higher in cases of B27 negative anterior uveitis without sacroiliac involvement. We were similarly also unable to show any difference within our group in the incidence of PiMZ with increased clinical severity of uveitis, bilaterality, or relapse, in contrast to the findings of Wakefield *et al.*[5]

One unusual finding which some workers[5,6] have also reported, but failed to comment on, is the relatively low incidence of the phenotype PiMS in anterior uveitis patients, as this is normally the next most frequently occurring phenotype (9·3%) after PiMM (86·5%) in the United Kingdom. As the genotype PiSS has been associated with severe deficiencies of α_1-antitrypsin in much the same way as PiZZ, it might be expected that the incidence of PiMS should also be increased in anterior uveitis. Our results, if anything, show a negative correlation of PiMS with acute anterior uveitis, possibly implying a protective role similar to that seen with some tissue types in other disease.[15]

The theory of a PiMZ association with anterior uveitis is an attractive one, as it provides a potential genetically determined immunochemical mechanism for disease susceptibility. It is becoming increasingly clear, however, that its potential role as a predisposing gene is at best part of a far more complex immunogenetic mechanism, and it might even be merely a marker for an alternative, as yet unidentified, gene. Chromosome 14 is known to contain several genes associated with immunoglobulins and their synthesis, and there has recently been some interest in the possible role of the IgG heavy-chain (Gm) allotypes in determining susceptibility to anterior uveitis. The gene locus for the Gm allotypes is on chromosome 14q, in close proximity to that of the Pi system,[16] with which it occurs in autosomal linkage,[17] and it was argued that the PiMZ phenotype was only a genetic marker for a specific Gm allotype.[18] An association between such specific allotypes and anterior uveitis has, however, since been refuted[19] and retracted.[20]

At present, research into the immunogenetics of acute anterior uveitis and other inflammatory diseases[21] has mainly served to emphasise the complexity of the systems involved and the likelihood that these are controlled through a multiplicity of endogenous and exogenous factors which have yet to be correlated with each other.

This study was supported by the Iris Fund for Prevention of Blindness Ltd, York House (Ground Floor), 199 Westminster Bridge Road, London SE1 7UT

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Correspondence

Chemical burns to the eye

SIR, Mr S J Morgan emphasises the need to distinguish between ammonia and antipersonnel or antirape sprays such as CS and Mace [1] From personal experience over the past 18 months I can describe a very simple and rapid method of differentiation

In a series of 17 patients who had been assaulted with a pungent fluid one had a strong smell of ammonia on his clothes and clinically had features of a grade 1–2 alkali burn The other 16 presented with the coughing, blepharospasm, lacrimation, and irritation of the eyes and exposed skin typical of antipersonnel agents. In attending these cases all those who approached within 1/3 m experienced mild transient irritation of their eyes and exposed facial skin. This did not require direct patient contact and disappeared as the patient's symptoms lessened Once experienced, it is very characteristic There was no detectable smell, as is found with ammonia

I attribute this phenomenon to the agent evaporating into the atmosphere round the patient Ocular examination in all 16 patients revealed only mild conjunctival hyperaemia and occasional punctate corneal staining

LUCILLA BUTLER

Birmingham and Midland Eye Hospital,
Church Street,
Birmingham B3 2NS

Reference

1 Morgan SJ Chemical burns to the eye causes and management *Br J Ophthalmol* 1987, 71: 854–7

SIR, I can only say that I have never experienced the symptoms of CS gas intoxication whether at first hand or by being in proximity to a patient so afflicted I am sure Miss Butler's observation is a valuable one when seeing a patient soon after an attack

S J MORGAN

The Eye Hospital,
Wilton Avenue,
Southampton SO9 4XW

Book review

Manual of Corneal Surgery. Eds WILLIAM E BRUNER, WALTER J STARK, A EDWARD MAUMENEE. Pp. 139. £27·50 Longman: Harlow, Essex 1987.

It should be self-evident that an author knows for whom his book is written It is by no means obvious that the editors of this small volume or their many eminent contributors are at all sure who will constitute their readership. It is perhaps impossible to condense the elements of corneal surgery into 135 pages; the result is a disappointing, over-abbreviated work The lack of detail or scientific background makes it of limited use to the working corneal surgeon, while the balance of the book would be inappropriate for an ophthalmologist in training, with three out of 13 chapters being devoted to refractive surgery, when some of the techniques (for example, hydrogel corneal inlays) are highly experimental Can it really be the case that American ophthalmic surgery has diverged so far from European practices?

Liberal use has been made of simple diagrams which are easy to follow The text, too, is clear and comprehensible, giving the impression that corneal surgery is simple It isn't I feel the authors have not done themselves justice with this book, but I am sure it will find a wide readership

COLIN M KIRKNESS

Notes

Hong Kong symposium

A Clinical Ophthalmological Symposium will be held at Hong Kong on 2–4 December 1988. Details from Dr Patrick C P Ho, c/o Secretariat Office, Room 810–814 Wing on Plaza, 62 Mody Road, Tsimshatsui East, Kowloon, Hong Kong

Implant lenses

The Seventh Intraocular Implantlens Council Meeting (EIIC) will be held on 27-31 August 1989 at Zurich, Switzerland, on soft IOLs in children, IOL pathology and complications, and high-tech surgery. Details from AKM Congress Service, PO Box CH-4005, Basel, Switzerland.

Ocular trauma

An International Congress on Ocular Trauma will be held at Tel Aviv, Israel, on 19-24 February, 1989. Further information from The Secretariat, PO Box 50006, Tel-Aviv 61500, Israel.

Retinitis pigmentosa

The 5th International Retinitis Pigmentosa Congress will be held at Melbourne, Australia, on 4-7 November 1988 Its purpose is to stimulate and develop research in the Asian-Pacific region. Details from Congress Convenor (Leonie Kelleher), 44A Oxley Road, Hawthorn, Victoria 3122, Australia.

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TABLE OF CONTENTS

ORIGINAL ARTICLES

Ocular syphilis in patients with human immunodeficiency virus infection *Michael S. Passo and James T. Rosenbaum*

Response of human immunodeficiency virus-associated uveitis to zidovudine *Patrick L Ferrell, M -H. Heinemann, Calvin W. Roberts, Bruce Polsky, Jonathan W M. Gold, and Alfred Mamelok*

Normal α-L-fucosidase and other lysosomal enzyme activities in progressive cone dystrophy *Vasiliki D. Stoumbos, Richard G. Weleber, and Nancy G. Kennaway*

Uveitis and diabetes mellitus *Aniki Rothova, Christina Meenken, Robert P J. Michels, and Aize Kijlstra*

Failure of preenucleation radiation to decrease uveal melanoma mortality *Devron H Char, Theodore L. Phillips, Yvonne Andejeski, J. Brooks Crawford, and Steward Kroll*

Acute frosted retinal periphlebitis *Robert C. Kleiner, Henry J. Kaplan, Jeffrey L Shakin, Lawrence A Yannuzzi, Hal H Crosswell, Jr., and Walter C McLean, Jr*

Ocular perforation from a retrobulbar injection *Mark E. Schneider, David E. Milstein, Ray T. Oyakawa, Richard R Ober, and Randy Campo*

Management of anterior chamber depth after trabeculectomy *William C Stewart and M. Bruce Shields*

The effect of omitting botulinum toxin from the lower eyelid in blepharospasm treatment *Bartley R Frueh, Christine C. Nelson, James F. Kapustiak, and David C. Musch*

Allergic lacrimal obstruction *Ted H. Wojno*

Combined viable composite grafting and eyelid sharing techniques to prevent blepharoptosis after extensive tumor excision *Allen M. Putterman and Michael E. Migliori*

Accommodation and convergence insufficiency with left middle cerebral artery occlusion *Kenji Ohtsuka, Hiroshi Maekawa, Makoto Takeda, Nobuharu Ueda, and Susumu Chiba*

Immunohistochemical evidence of heterogeneity in macular corneal dystrophy *C Julia Yang, Nirmala SundarRaj, Eugene J.-M. A. Thonar, and Gordon K. Klintworth*

Visual results after keratoplasty in patients with posterior chamber intraocular lenses *Michael S. Insler, Craig J. Helm, and Herbert E. Kaufman*

Topical imipenem therapy of aminoglycoside-resistant *Pseudomonas* keratitis in rabbits *Mark R Sawusch, Terrence P. O'Brien, Joan Valentine, James D Dick, and John D. Gottsch*

Ocular findings in partial trisomy 10q syndrome *Kimberly Neely, Marilyn B Mets, Paul Wong, and Katrina Szego*

EDITORIAL

Counselling the patient with a posterior uveal melanoma *Jerry A. Shields*

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Contents

Effect of single-dose invermectin therapy on human *Onchocerca volvulus* infection with onchocercal ocular involvement HENRY S NEWLAND, ALBERT T WHITE, BRUCH M GREENE, SALVATORE A D'ANNA, EZATOLLAH KEYVAN-LARIJANI, MOHAMMED A AZIZ, P NOEL WILLIAMS, AND HUGH R TAYLOR *page* 561

Retinal burns caused by exposure to MIG-welding arcs: report of two cases G P H BRITTAIN *page* 570

Retinoblastoma in Great Britain 1969-80: incidence, treatment, and survival B M SANDERS, G J DRAPER, AND J E KINGSTON *page* 576

N-3-pyridylmethyl-N′-*p*-nitrophenylurea ocular toxicity in man and rabbits JOEL S MINDEL, ALEX B KHARLAMB, ALAN H FRIEDMAN, JOHN H KARAM, ROBERT D STONE, AND IRWIN M SIEGEL *page* 584

Confidence intervals for change in automated visual fields H DUNBAR HOSKINS, SCOTT D MAGEE, MICHAEL V DRAKE, AND MARTIN N KIDD *page* 591

Dopamine-2 receptor blockade does not affect the ocular hypotensive action of timolol QAIS A MEKKI AND PAUL TURNER *page* 598

Long-term visual results after pars plicata lensectomy-vitrectomy for congenital cataracts STEPHEN A GROSSMAN AND GHOLAM A PEYMAN *page* 601

A 10-year survey of penetrating eye injuries in Gwent, 1976-85 W N WYKES *page* 607

Choroidal osteoma presenting in pregnancy B K MCLEOD *page* 612

Short-term effects of neodymium-YAG transscleral cyclocoagulation in patients with uncontrolled glaucoma O BADEEB, G E TROPE, AND C MORTIMER *page* 615

Cavernous haemangioma presenting as an orbital mass after enucleation for a choroidal melanoma: case report A N HARNETT, P THORPE, AND J HUNGERFORD *page* 618

Bilateral tears of the retinal pigment epithelium KAZUMI NOROSE, TSUYOSHI TANINO, AND KATSUZO SEGAWA *page* 621

Infectious crystalline keratopathy C B JAMES, P J MCDONNELL, AND M G FALCON *page* 628

Globe luxation in histiocytosis X C M WOOD, A D J PEARSON, A W CRAFT, AND J W HOWE *page* 631

Floppy eyelid syndrome associated with keratotorus ALEKSANDAR PARUNOVIĆ AND BOŽIDAR ILIĆ *page* 634

α_1-Antitrypsin phenotypes in acute anterior uveitis I R FEARNLEY, D J SPALTON, A MILFORD WARD, B SLAVIN, AND F MUNCEY *page* 636

Correspondence *page* 640

Book review *page* 640

Notes *page* 640

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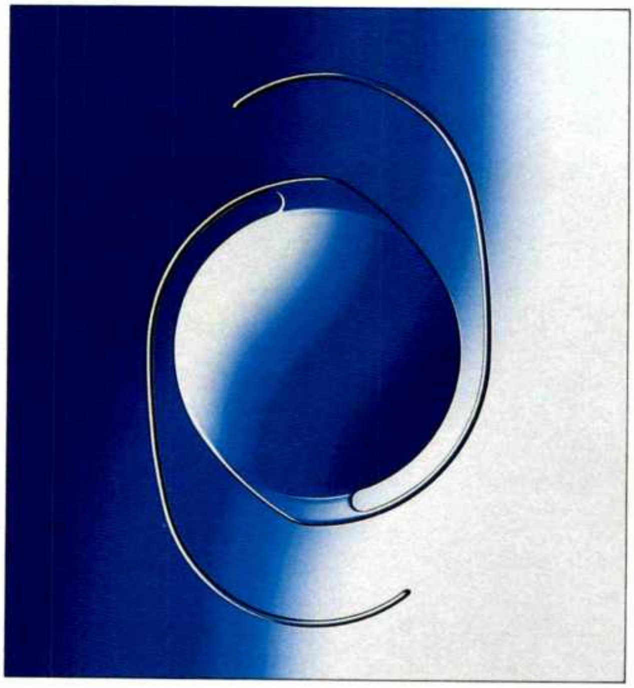

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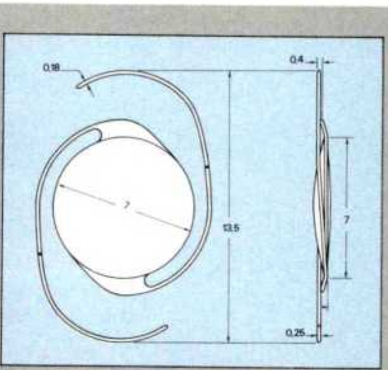

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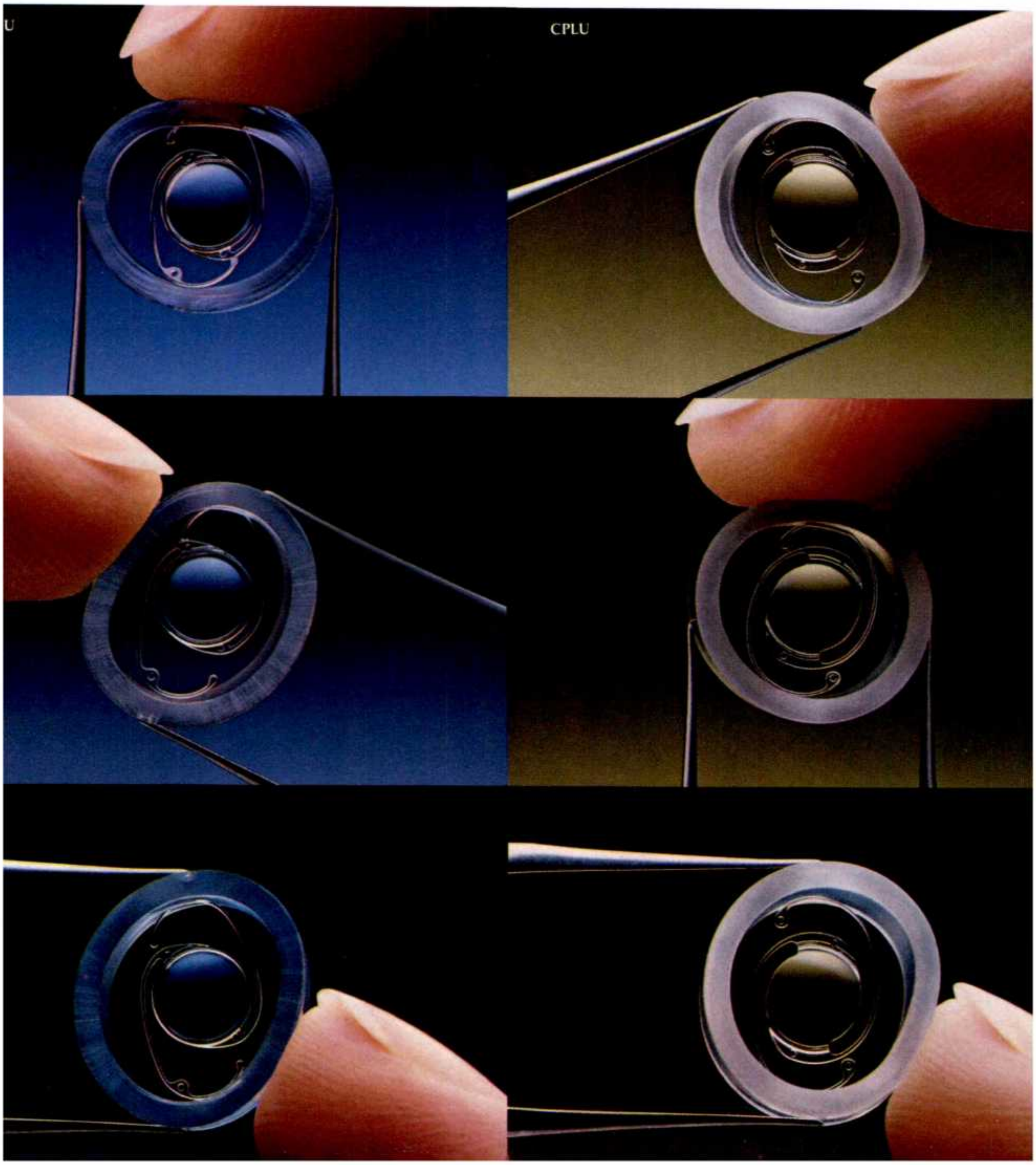

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British Journal of Ophthalmology, 1988, 72, 641–645

Photostress recovery in chronic open angle glaucoma

MARK D SHERMAN AND PAUL HENKIND*

From the Department of Ophthalmology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York, USA

SUMMARY Photostress recovery time was measured in 30 eyes from 15 patients with chronic open angle glaucoma, and 30 eyes from 15 individuals of a similar age group with no ophthalmological disorder. The average recovery time in patients with glaucoma was 70·47 (SD 35·39) seconds. The average recovery time in the control population was 41·97 (SD 17·34) seconds. This difference was statistically significant ($p<0·001$). There was a small positive correlation between age and recovery time in the control population, whereas there was no correlation between age and recovery time in the glaucoma group. There was no correlation between visual acuity and recovery time for either group. There was also no correlation between intraocular pressure and recovery time for the glaucoma group. It was not possible to control for pupillary dilatation in this study. However, it has been previously demonstrated that pharmacological meiosis will not delay photostress recovery time in normal subjects. This is the first report of photostress recovery testing in patients with chronic open angle glaucoma. The results are discussed in terms of the pathophysiology of glaucoma and previous photostress studies in patients with macular disease.

Photostress recovery time (PSRT) has frequently been used as a quantitative measure of macular function. Initially described by Magder[1] as a clinically useful tool for following the progression of central serous retinopathy, photostress recovery has also been utilised in the study of the ocular toxicity of antimalarial medications,[2] ocular toxicity of birth control pills,[3] and various macular and optic nerve diseases.[4-7] Although a precise pathophysiological explanation for aberrant photostress responses has yet to be offered, it has been clearly demonstrated that optic nerve and macular disease can be differentiated on the basis of PSRT, where the retina with macular disease has an increased recovery time and that with optic nerve disease has a normal recovery time.[7]

A major criticism of photostress recovery testing has been the lack of a standardised technique in conducting the test. The test consists in measuring the visual acuity of a given eye, illuminating that eye with a high intensity light for a specific length of time—creating a central scotoma—and measuring the time required for the eye to return to baseline visual acuity once the illumination period is over. The time required to return to baseline acuity is recorded as the photostress recovery time. The photostress response is not entirely understood but has been explained as a transient state of visual insensitivity caused by bleaching of the visual pigments of the retina.[7] Return of sensitivity is dependent on resynthesis of the visual pigments, and resynthesis requires adequate perfusion of the photoreceptors and the pigment epithelium. The process is independent of optic nerve integrity.

In order to standardise the approach and simplify the implementation of photostress testing a hand held instrument was designed to measure photostress recovery time.[8] With this instrument, called a scotometer, the toxic effects of antimalarial medications on the retina, as manifested by an increased recovery time, were demonstrated.[2] This instrument has also been used to demonstrate the toxic effects on the retina of birth control pills.[3] Glaser *et al.* used an ordinary penlight for an illumination period of 10 seconds to compare recovery time in patients with macular disease and optic nerve disease.[7] They found a small increase in recovery time with increasing age in both groups and defined a normal recovery time as

---

*Deceased

Correspondence to Mark D Sherman, MD, Department of Ophthalmology, University of Arizona Health Sciences Center, Tucson, Arizona 85724, USA

less than 50 seconds. Patients with macular disease (senile macular degeneration, submacular drusen without serous detachment, diabetic retinopathy, cystoid oedema) had an average recovery time greater than 150 seconds; eyes with optic nerve disease (optic neuritis, optic atrophy, ischaemic optic neuropathy, lymphomatous infiltrations) had recovery times of 50 seconds or less. The authors concluded that photostress recovery testing was 'a valuable adjunct in the clinical assessment of decreased vision and a sensitive discriminator between occult optic neuropathy and subtle maculopathy.'[7]

The following study presents the results of photostress recovery testing in patients with chronic open angle glaucoma and patients of a similar age group having no ophthalmological disorder.

Subjects and methods

We prospectively studied photostress recovery time in patients with chronic open angle glaucoma (COAG) being followed up at the Glaucoma Clinic of Montefiore Hospital, and patients from the General Eye Clinic with no known ophthalmological disorder. The ophthalmoscope was recharged before each testing period for at least eight hours. The photostress test was performed before any pharmacological preparation for routine ocular examination. Photostress testing was conducted as follows:

(1) Best corrected visual acuity was determined for each eye with Snellen test letters at a distance of 6 m (20 feet). All subsequent measurements were obtained with the same chart, under the same lighting conditions, and by the same investigator. All eyes were undilated. Because of the limited number of large test letters on the Snellen chart and the possibility of consequent inaccuracy of measurements, the data were considered invalid for eyes with visual acuity less than 6/30 (20/100) and were eliminated from the analysis.

(2) The right eye was tested first, with the left eye covered by an opaque shield. The patient was instructed to look directly into the halogen bulb attachment of a Welch Allyn halogen bulb ophthalmoscope, which was held 2 to 3 cm from the eye for an illumination period of 10 seconds.

(3) Immediately after the light was removed the patient was instructed to read the Snellen chart, starting at the first visible line and continuing to increasingly smaller lines as they became clear. The recovery time was recorded as the time (in seconds) required for the patient to read correctly three letters of the line just above that recorded as best visual acuity. Recovery time was recorded to a maximum of 150 seconds.

(4) The same procedure was then conducted for the left eye, with the right eye occluded.

Intraocular pressure was measured for the COAG group with a non-contact air tonometer. After being photostress tested each patient received a routine ophthalmological examination from an ophthalmologist who was not aware of the patient's photostress scores. Each patient's chart was later reviewed for data on visual field defects, systemic disease, medication history, and previous ophthalmological procedures and findings. Each control patient had a normal anterior and posterior eye.

Results

Only data from patients who were capable of having both eyes tested were included in the data analysis. The COAG group consisted of patients with a diagnosis of glaucoma in both eyes. The photostress recovery time for each eye of a given patient was averaged to provide a single photostress score for that patient.

Table 1 summarises the clinical data for patients in

Table 1 *Clinical data for patients with glaucoma*

Age (yr), sex	*Eye*	*Visual acuity*	*Intraocular pressure (mmHg)*	*PSRT* (s)*	*Recovery score† (s)*
73, F	OD	20/70	16	150	150
	OS	20/50	14	150	
78, F	OD	20/50	12	42	62
	OS	20/40	15	82	
44, F	OD	20/25	14	28	74
	OS	20/25	13	120	
78, F	OD	20/40	18	32	32 5
	OS	20/30	20	33	
72, M	OD	20/40	9	35	66
	OS	20/30	11	97	
77, F	OD	20/30	15	19	72
	OS	20/25	15	125	
77, M	OD	20/40	21	48	53
	OS	20/30	19	58	
71, M	OD	20/70	22	150	111
	OS	20/50	30	72	
74, M	OD	20/30	15	42	42
	OS	20/30	18	42	
51, M	OD	20/25	16	43	32
	OS	20/25	19	21	
76, F	OD	20/40	21	88	59
	OS	20/30	15	30	
68, F	OD	20/30	14	22	39
	OS	20/30	14	56	
63, M	OD	20/50	29	81	115 5
	OS	20/50	25	150	
56, F	OD	20/25	33	50	41
	OS	20/25	21	32	
66, M	OD	20/25	NA‡	73	108
	OS	20/25	NA	143	

*Photostress recovery time
†Average PSRT
‡Not available

Table 2 *Clinical data for control patients*

Age (yr), sex	*Eye*	*Visual acuity*	*PSRT* (s)*	*Recovery score† (s)*
67, M	OD	20/70	20	34
	OS	20/50	48	
60, M	OD	20/30	45	34
	OS	20/30	23	
68, F	OD	20/30	35	33·5
	OS	20/30	32	
79, F	OD	20/30	79	96 5
	OS	20/30	114	
67, F	OD	20/25	31	34
	OS	20/25	37	
60, M	OD	20/25	20	33
	OS	20/30	46	
51, M	OD	20/25	22	21 5
	OS	20/20	21	
56, M	OD	20/25	45	41
	OS	20/25	37	
60, F	OD	20/25	47	36·5
	OS	20/25	26	
51, M	OD	20/25	57	40 5
	OS	20/20	24	
50, F	OD	20/30	53	40
	OS	20/30	27	
48, F	OD	20/40	25	30
	OS	20/25	35	
66, F	OD	20/30	25	51·5
	OS	20/30	78	
51, F	OD	20/25	59	54
	OS	20/25	49	
50, F	OD	20/30	55	49 5
	OS	20/25	44	

*Photostress recovery time
†Average PSRT

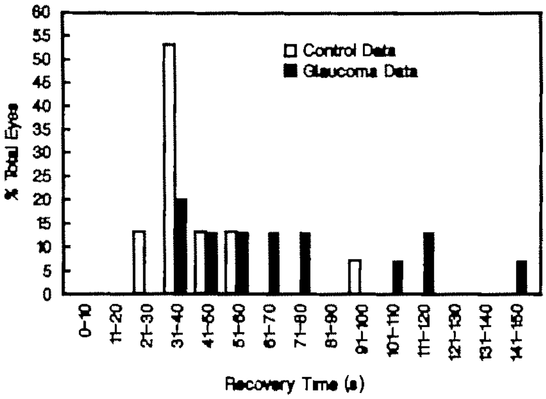

Fig 1 *Distribution of photostress recovery scores from 15 patients with chronic open angle glaucoma and 15 patients with normal eyes*

the COAG group. The average recovery score for patients in this group was 70·47 seconds, SD 35·39 seconds. The average age of patients in this group was 68·27 years, SD 10·52 years. The correlation between recovery score and age did not reach statistical significance in this group ($r=0{\cdot}32$, $p>0{\cdot}05$). The average intraocular pressure was 17·75 (SD 5·01) mmHg. The correlation between intraocular pressure and recovery score was not statistically significant. Likewise the correlation between visual acuity and recovery score was not statistically significant.

Table 2 summarises the clinical data for patients in the control group. The average photostress recovery score for patients in the control group was 41·97 seconds, SD 17·34 seconds. The difference in recovery time between the control group and the glaucoma group was significant ($p<0{\cdot}001$). Fig. 1 illustrates the distribution of photostress recovery scores.

The average age of patients in the control group was 58·93 years, SD 9·04 years. The difference in age between the COAG group and control group was not statistically significant. There was a weak correlation between recovery score and age in the control group ($r=0{\cdot}41$, $p<0{\cdot}05$). Fig. 2 illustrates photostress scores as a function of age. Repeat photostress testing on subsequent clinic visits for a subset of patients showed the test results were reproducible. Table 3 summarises the photostress results for glaucomatous and normal patients

Discussion

Magder described photostress evaluation as being specific for diagnosing oedema of the macular area.[1] He proposed that in central serous retinopathy, where there is a separation between the pigment epithelium and neuroepithelium, normal chemical reactions between these layers cannot occur, resulting in a delayed responsivity to light in the photostress test. Severin *et al.*[9] explained the photostress response in terms of bleaching and resynthesis of the visual pigments. They proposed that any pathological state which interferes with the ability of the photoreceptors to resynthesise photopigment, either by interrupting enzymatic steps in the biochemical cycle or by altering anatomical relationships, will effect the performance reserve of the retina, as shown by the photostress recovery test.

Table 3 *Summary of photostress test results*

Group	*Patient no*	*Mean age (yr)*	*Mean recovery score (s)*	*Correlation (r) of age vs recovery score*
Normal	15	58·93±9·04	41 97±17 34	0·41*
Glaucoma	15	68 27±10·52	70 47±35·39	0 32†

*Statistically significantly at $p<0{\cdot}05$
†Not statistically significant
±=Standard deviation.

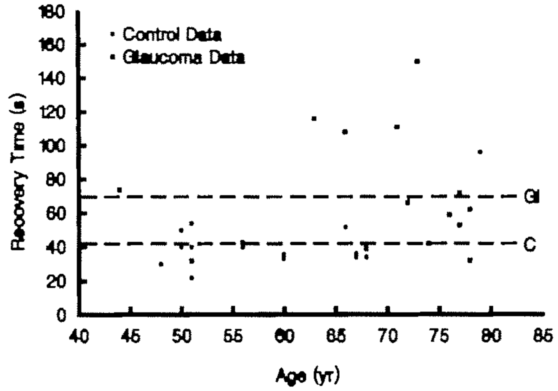

Fig. 2 *Photostress recovery score versus age in 15 patients with chronic open angle glaucoma and 15 patients with normal eyes.*

In cases where the disease state has already caused destruction of the photoreceptors the signs may be obvious, manifesting as a change in visual acuity, colour vision, visual field, or an abnormal retina. However, when the disease is incipient or its effects subtle, there may be no noticeable change in vision or deterioration on routine examination. In these cases aberrant photostress recovery times may be the first sign of pathological activity.

In the present study we found a statistically significant increase in photostress recovery time in patients with chronic open angle glaucoma as compared with normal patients of a similar age group with no ophthalmological disorder. There was no significant correlation between intraocular pressure and recovery time. The majority of the glaucoma patients had their pressure under control at the time of the study. However, when one examines the distribution of recovery times in Fig. 1, a broader range of scores for the glaucoma group is observed. This greater range of scores may indicate that different pathological stages were being tested. The increased scores of the glaucoma patients cannot be explained by the age of this population, as the difference in age between the glaucoma group and control group was not statistically significant.

It was not possible to correlate photostress response with medical therapy for glaucoma in this study. There were not enough patients on a single drug regimen to allow unbiased conclusions to be drawn. Several investigators have addressed the question of the effect of pupillary dilatation on photostress recovery.[4,10-13] These authors have consistently arrived at the conclusion that pupillary dilatation has little or no effect on recovery time. The explanation for this observation is that the iris of the meiotic pupil reduces the luminous intensity only in the extramacular region, whereas the photostress stimulus tests the physiological integrity of the macula itself[11] Ulla *et al.* recently considered the effect of pharmacological alteration in pupillary size on macular recovery time.[12] They reported that pharmacological mydriasis had no effect, whereas pharmacological meiosis *reduced* the recovery period in a group of normal patients. Certainly this point deserves further investigation given the results of the present study.

All of the patients in the glaucoma group had some form of visual field defect. Only one previous study of photostress recovery has considered the issue of visual fields.[13] Severin *et al.*, using an elaborate apparatus for retinal dazzling, examined 14 cases of maculopathy of various aetiologies, and recorded each patient's visual field with his or her recovery time.[13] Their data are unfortunately inconclusive in terms of relating aberrant recovery times to field defects However, they did observe markedly increased recovery time both in patients with a central scotoma (secondary to central serous retinopathy) and in a patient with a ring scotoma (secondary to chloroquine maculopathy). They did not test any patients with glaucoma.

It has been suggested that increased photostress recovery times may result from anatomical derangement in the area of the macula or decreased perfusion of the photoreceptors.[7] In previous studies of photostress recovery, increased recovery scores have been clearly related to pathological separation of cell layers of the retina. It seems reasonable to assert that any disease that causes damage to the photoreceptors, pigment epithelium, Bruch's membrane, choriocapillaris, or vascular supply to the macula may alter the photostress recovery time. Certainly further investigation is necessary to explain the pathophysiological basis for delayed photostress recovery in patients with glaucoma.

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Birdshot chorioretinopathy: clinical characteristics and evolution*

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SUMMARY During the period 1980–6 102 patients from 14 European eye clinics were diagnosed as having birdshot chorioretinopathy (BSCR). All were Caucasian, and the series consisted of 47 men and 55 women, with a mean age of 52·5 years. The major findings in this rare disorder concern the ocular fundus. Most marked are the patterned distribution of depigmented spots without hyperpigmentation, radiation from the optic disc in association with vitritis, retinal vasculopathy with frequent cystoid macular oedema, and involvement of the optic nerve head. The distribution and appearance of the lesions suggest that they are related to the major choroidal veins. Complications of the disease were epiretinal membranes, retinal neovascularisation, recurrent vitreous haemorrhage, subretinal neovascular membranes occurring both in the juxtapapillary and macular regions, and optic atrophy. The medical history was not contributary. HLA testing showed very strong disease association with HLA A29 (95·8%). The evidence suggests that it is a single disease entity rather than a group of disorders because of the remarkable similarity in the ophthalmological appearance and the clinical course, combined with the exceptionally high association with HLA A29.

In 1980 a rare ocular disease was described by Ryan and Maumenee.[1] In the absence of a known aetiology, they chose the descriptive name 'birdshot retinochoroidopathy' inspired by the unusual picture, which showed multiple small, cream coloured lesions, scattered mainly around the optic disc and radiating towards the equator, without hyperpigmentation at the level of the retinal pigment epithelium. Because of the presence of vitritis, retinal vasculitis, and cystoid macular oedema they likened the disease to pars planitis, but emphasised the absence of snowbanking over the pars plana.

Other descriptive names have been used for this

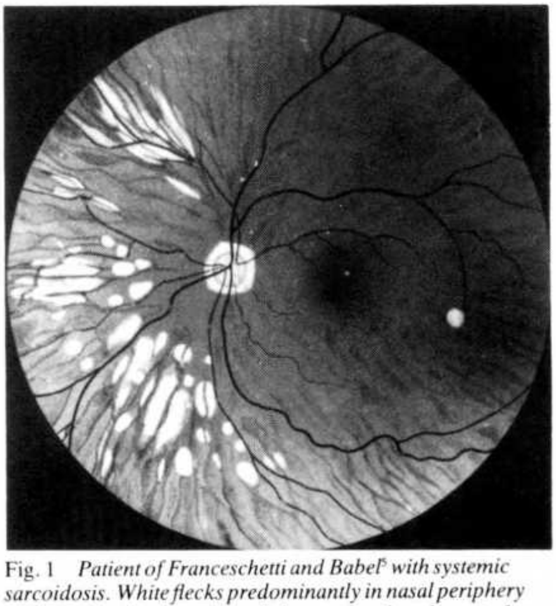

Fig. 1 *Patient of Franceschetti and Babel[5] with systemic sarcoidosis. White flecks predominantly in nasal periphery and round optic disc with radial pattern and tendency to form lines towards periphery. (By permission of the Fondation Professor A Franceschetti.)*

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*This paper is the result of a collaboration by the following members of the European Fluorescein Angiography Club: P Amalric (Albi, France); M Spitznas (Bonn, FRG); C Orsini Dupont (Caen, France); G Coscas, A Gaudric, G Soubrane (Créteil, France); J J de Laey, H A Priem (Gent, Belgium); J Hooymans, Z Timmerman (Groningen, The Netherlands); J A Oosterhuis, A H Renger-van Dijk (Leiden, The Netherlands); A Leys, B Snyers (Leuven-Louvain, Belgium); A Bird, R Blach, Z Gregor, A M Hamilton, D Sharp, J Shilling (London, England); A F Deutman (Nijmegen, The Netherlands); J A Bernard, G Quentel (Paris, France); G S Baarsma, P T V M de Jong, B C P Polak (Rotterdam, The Netherlands).

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entity, such as 'vitiliginous chorioretinitis' by Gass,[2] who stressed the similarity of the fundus patches to cutaneous vitiligo, 'salmon-patch choroidopathy' by Aaberg,[3] and 'choriorétinopathie en grains de riz' by Amalric and Cuq,[4] who saw a similarity to the rice grain pattern.

Probably the first description of birdshot chorioretinopathy (BSCR) in the early literature occurred in 1949 in a case report by Franceschetti and Babel.[5] They described a 63-year-old woman with a condition they named 'choriorétinopathie en taches de bougie' (candlewax spots), who had systemic features of sarcoidosis. On ocular examination she had minimal involvement of the anterior segment with only minute keratic precipitates (KP) but had dense vitreous opacity. The authors described a pale optic disc, very narrow retinal vessels, and multiple white 'retinal and chorioretinal' spots, and stressed the absence of pigmentation of the spots (Fig. 1). Later they saw areas of choroidal atrophy appear in the inferonasal quadrant. All these features are characteristic of BSCR.

Other authors have highlighted special characteristics of BSCR such as distinctive electrophysiological abnormalities,[6] its association with the HLA A29 gene,[7] and the occurrence of complications such as subretinal neovascular membranes[8,9] and optic atrophy.[12] The association with a rhegmatogenous retinal detachment has also been reported.[1,6,10,11] More case reports followed[12–17] dealing with small numbers of patients only, giving the overall impression that BSCR is a rare disease.

In this study we analyse in a large series of patients the entity known as birdshot chorioretinopathy (BSCR) as defined by the accepted clinical picture. In particular, we sought to determine whether or not this is a single clinical entity or simply a collection of exotic cases with similar appearance.

Subjects and methods

The patients were collected from 14 ophthalmological departments in five European countries. The minimum criteria used for patient selection were based on the clinical manifestations as described by Ryan and Maumenee.[1] Each patient was required to have the typical cream coloured birdshot spots with a symmetrical appearance in both eyes (if asymmetrical, then one eye should at least be very characteristic of BSCR in number, size, and distribution of the lesions), together with one of the following features: evidence of retinal vasculopathy, evidence of disc oedema or optic atrophy, or presence of vitreous cells.

The patients consisted of 47 men aged 23–79 years (average 50·7 years) and 55 women aged 32–74 years (average 54·4 years). All were Caucasian. They were examined both clinically and by colour photography and fluorescein angiography (Table 1). The clinical files and the photographic documentation were studied by one of us (HAP).

The first set of data included the general history, with specific reference to skin disease, allergy, and hearing loss; and the ocular history, which covered previous eye disease, surgery, and family history. The second set of data concerned the clinical examination, including visual acuity, findings on slit-lamp examination, tonometry, and ophthalmoscopy. The third described the fluorescein angiographic findings. The fourth dealt with additional investigations such as colour vision tests, perimetry, dark adaptation, electro-oculogram (EOG), electroretinogram (ERG), visually evoked potentials (VEP), and HLA typing. Finally, long term behaviour and the influence of treatment were assessed.

Table 1 *Clinical and functional investigations*

	Number of BSCR patients involved
Total number in study	102
Fundus pictures	102
Fluorescein angiography	102
Medical history	71
Ocular history	79
Slit-lamp	68
Tonometry	60
Visual acuity	94
Colour vision tests	31
Perimetry	43
Dark adaptation tests	24
EOG and ERG	42
VEP	30
HLA typing	48 (in 5 patients A29 only)

Table 2 *Medical history in 71 BSCR patients*

	No of patients
Arterial hypertension	16
Cardiac disease	5
Cerebrovascular accident	2
Rheumatic disease, arthritis	6
Low backache	2
Gout	1
Allergy (penicillin, fluorescein)	6
Eczema, psoriasis	4
Hirsutism	1
Vitiligo (only in summer season)	1
Hearing loss	3
Menière's disease	1
Migraine	1
Infectious disease	
tuberculosis	2
viral hepatitis	2
pericarditis	1
sarcoidosis	1

Results

The study comprised 203 eyes of 102 BSCR patients; one eye with an extensive corneal leucoma since childhood preventing fundus examination was not included. Full information on the clinical and functional investigations were not always available at the time of collection of the material (Table 1).

MEDICAL AND OCULAR HISTORY

A full medical history was recorded for 71 patients, but in most cases no relevant general disorder was identified (Table 2). In one patient with hilar lymphadenopathy the diagnosis of sarcoidosis was confirmed by biopsy and a positive Kveim test. Sarcoidosis was specifically sought in 38 other patients but was negative in all. The incidence of arterial hypertension in 16 patients, coronary artery disease in 5, cerebrovascular accident in 2, and retinal vein obstruction in 3 was higher than one would expect in a similar age group.

With the exception of a rather high incidence of open angle glaucoma there were no apparent ocular disorders associated with BSCR (Table 3).

A variety of ocular conditions were identified in family members but none of them showed evidence of BSCR. The dizygotic twin sister of a 52-year-old female patient was extensively examined; one sister had blood group AB+ and the other one A+, although both were identical HLA types. The twin sister had normal visual acuity in both eyes and no ocular complaints. Funduscopy revealed marked arteriosclerosis and two small perivascular haemorrhages but no signs of BSCR.

On assessment of the diagnosis BSCR, many patients already had a long history of visual symptoms (Table 4). Blurred vision and floaters were the most common complaints.

CLINICAL EXAMINATION

Visual acuity

There was a wide range of visual acuity on assessment of the diagnosis BSCR. However, most eyes (73%) had a visual acuity of 6/18 or better (Table 5).

In many patients the diagnosis BSCR was not made initially, since the clinical picture did not become well known until 1980. The significance of the good visual acuity at the time of diagnosis is therefore greater when evaluated in relation to the duration of ocular symptoms (Table 6). Out of 84 eyes 33 had a visual acuity of 6/26 or less when ocular complaints had been present for more than one year.

Table 3 *Ocular history in 79 patients with BSCR*

	Eyes
Open angle glaucoma	16 (1 eye Scheie operation)
Secondary glaucoma	2 (2 trabeculectomies)
Cataract extraction	5 (3 ECCE with IOL, 2 ICCE)
Rhegmatogenous retinal detachment	2
Aphakic retinal detachment	1
Peripheral retinal breaks	1
Central retinal vein occlusion	1
Branch vein occlusion	2
Chloroquine keratopathy	1
Corneal leucoma (unknown aetiology)	1

Table 4 *Oculat symptoms at onset (81 BSCR patients)*

	No of patients
Blurred vision	58
Floaters	30
Night blindness	8
Distorted vision	4
Photopsia	4
Irritation	4
Pain	2

Table 5 *Visual acuity at initial ascertainment of BSCR*

	Eyes	
	No	%
6/7·5 or more (0 8 or more)	73	39
6/18–6/9 (0·4–0·7)	64	34
6/60–6/24 (0·1–0·3)	35	19
<6/60 (<0·1)	15	8
Total	187 eyes*	100%

*One eye not in study

Anterior segment and vitreous

Details of the anterior segment were obtained in 68 patients. Only two of them showed redness of one or both eyes and signs of acute inflammation of the anterior segment. Eight patients had bilateral fine pigmented KP, and eight had very mild flare and cells in the anterior chamber of both eyes. In 13 eyes lens opacities were present but did not prevent adequate

Fig 2 *Clinical manifestations of birdshot chorioretinopathy* A and B. *Patients aged 56 years (Gent) Typical symmetrical fundus pictures of BSCR Small neovascular tuft at inferior margin of optic disc (arrow in B).* C· *Same fundus as in B Radial linear structures in nasal periphery. Large choroidal vessels run over the lesions (arrow).* D· *Patient aged 37 years (Leiden). Large area of juxtapapillary atrophy with increased visibility of major choroidal vessels* E. *Patient aged 51 years (Leiden) Sheathing of retinal vessel (arrow).* F: *Patent aged 64 years (Gent). Left fundus of BSCR patient with ocular history of 10 years' duration. The optic disc is pale, the retinal vessels are irregular and narrow, small haemorrhages are present.*

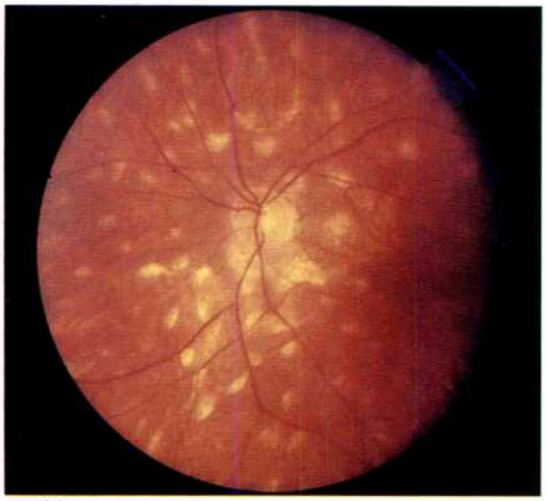


Fig. 2A

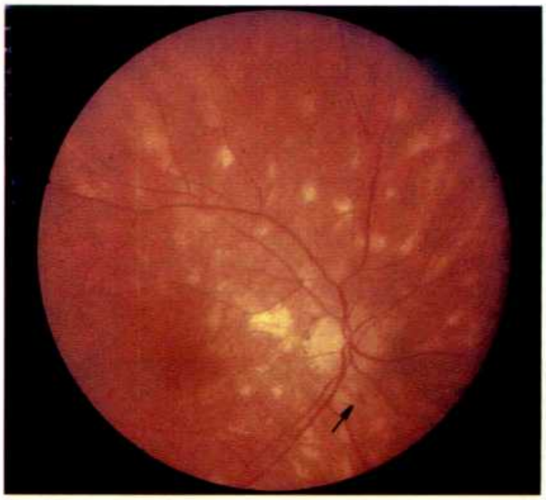
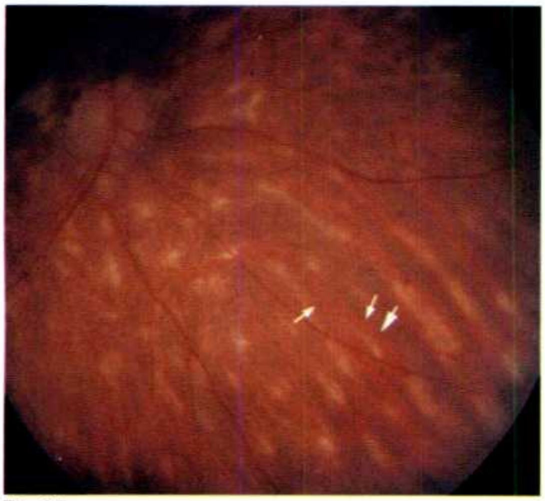


Fig. 2B



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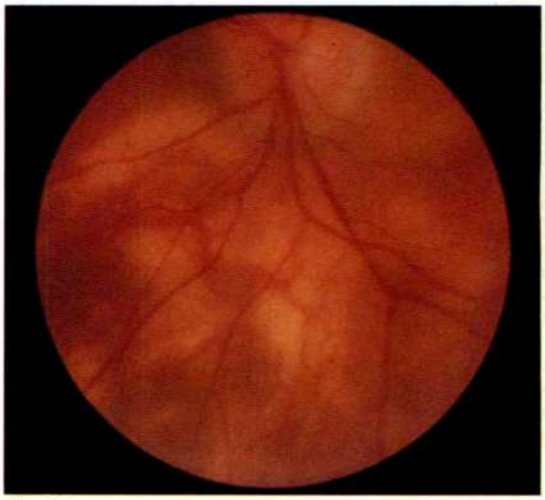

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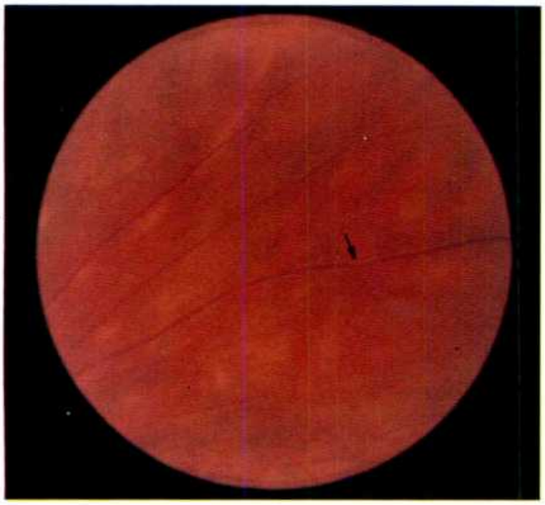

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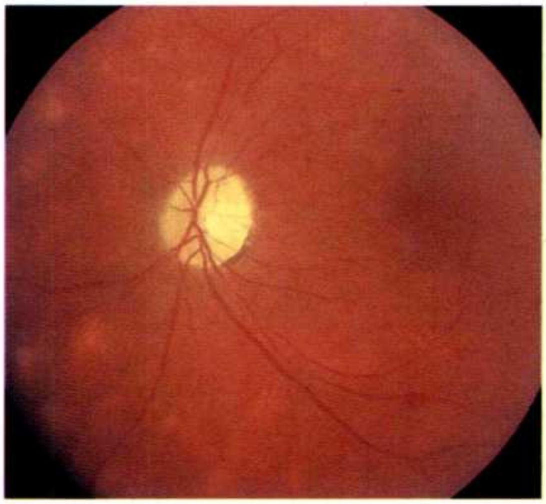

Fig. 2F

fundus examination. In 80 patients (159 eyes) examination of the vitreous was recorded: cells were seen in 121 eyes (76·1%) and opacities in 73 eyes (45·9%). In total, signs of vitreous involvement were present in 83% of the eyes examined.

Ophthalmoscopic and fluoroangiographic findings

Choroidal lesions. In 91 patients both eyes were symmetrically involved (colour plate 2A, B) whilst in 11 patients the condition was markedly asymmetrical. The following aspects of the lesions were considered: appearance, distribution, and fluoroangiographic behaviour.

In most eyes the lesions were remarkably uniform in colour, shape, and size (158 eyes, 77·8%). Most frequently they were oval, with the longest diameter directed towards the optic disc and a diameter of less than ¼ disc diameter (DD); they had a cream

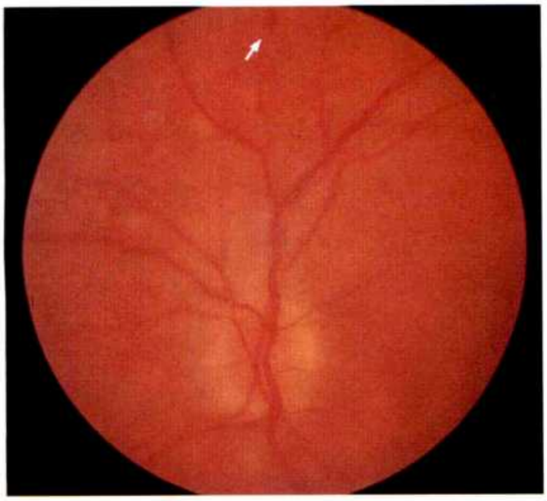
Fig. 3A

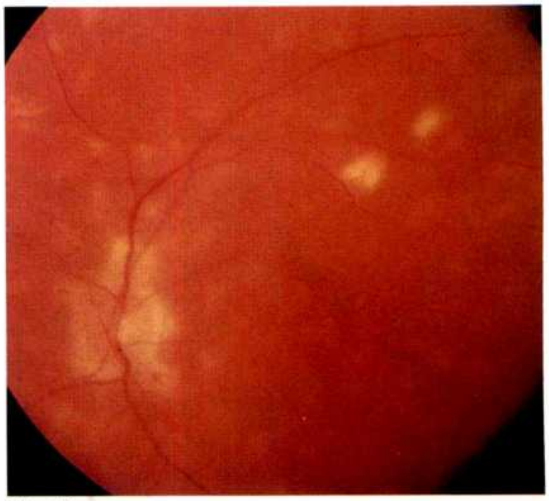
Fig. 3B

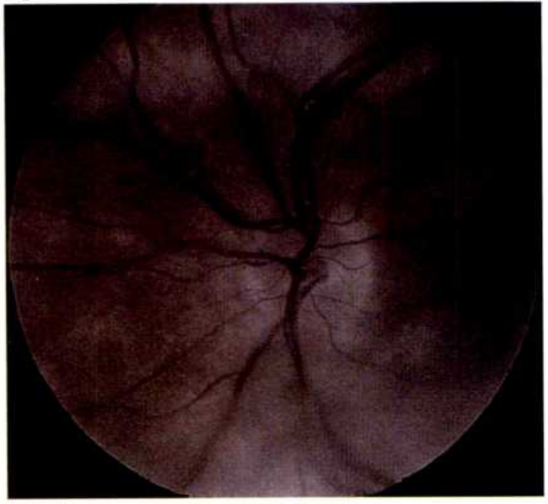
Fig. 3C

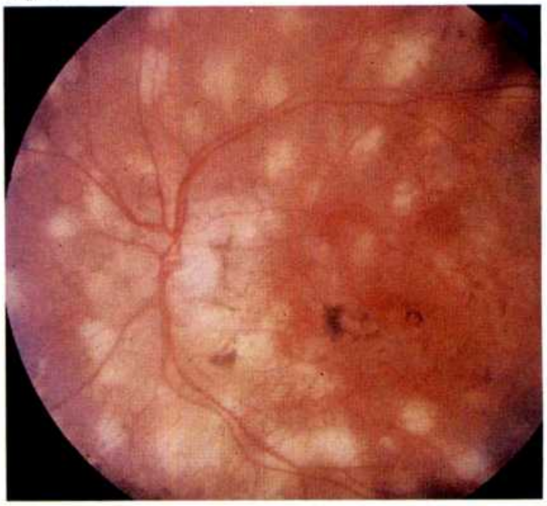
Fig. 3D

Fig. 3 *Evolution of birdshot chorioretinopathy.* A: *Patient aged 44 years (Gent). Right eye in 1975, diagnosed as bilateral papillouveitis. Note disc oedema, retinal haemorrhage (arrow). BSCR flecks are hardly visible.* B: *Same fundus as A in 1985: pale optic disc, narrow vessels, marked juxtapapillary lesions; the birdshot flecks have become more clearly visible.* C: *Patient aged 34 years (Gent). Right eye in 1972 showing swollen optic disc; diagnosis: bilateral papillouveitis.* D: *Same fundus as C in 1985 (courtesy of B Snyers, Louvain), clearly showing birdshot flecks, narrowed arteries, small darkish dots as possible sign of redistribution of pigment.*

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Use of the 0.6% strength is only recommended in patients who are not controlled on the lower strengths of Glauline.

CONTRA-INDICATIONS, WARNINGS ETC.

The use of Glauline is not recommended in patients with obstructive airway disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Glauline should only be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block. Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards. No clinical trials in children have been carried out. Glauline should not be used in patients fitted with soft (hydrophilic) contact lenses.

PHARMACEUTICAL PRECAUTIONS

Glauline should not be diluted or dispensed from any container other than the original bottle. It is potent for three years unopened, but as with other eye drops the contents of each bottle should be discarded one month after opening.

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FURTHER INFORMATION

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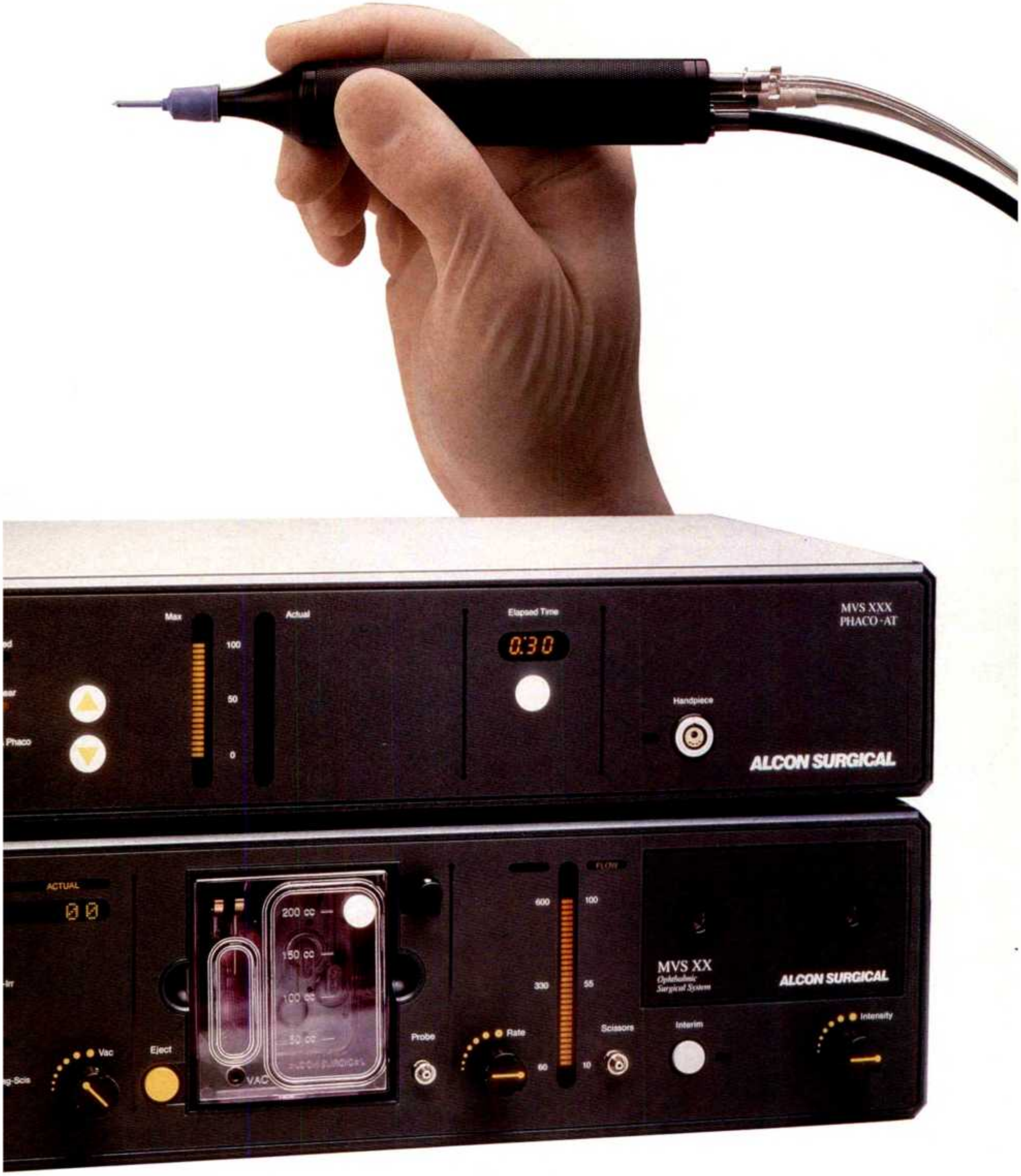

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Table 6 *Initial visual acuity and length of ocular history*

Length of history at initial ascertainment	*Visual acuity (number of eyes)*			
	6/7·5+	*6/9–6/18*	*6/24–6/60*	*<6/60*
4 weeks or less	15	4	1	
1–5 months	15	7		
6–11 months	14	10	6	1
1–4 years	7	25	14	6
5 years and more	11	8	8	5
History not mentioned	11	10	6	3
Total	73	64	35	15

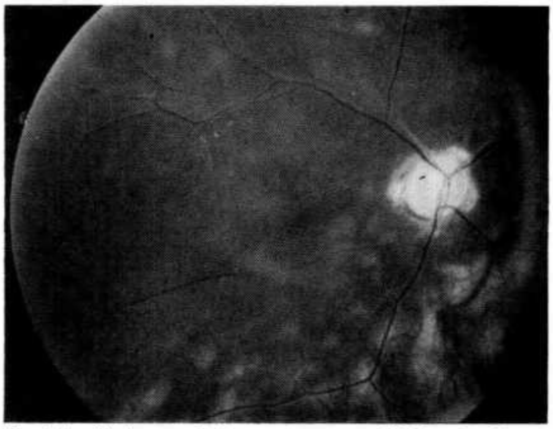


Fig. 4A *Patient aged 51 years (courtesy of University Eye Clinic, Créteil). BSCR patient with petaloid aspect of optic disc due to lesions at the margin, sheathing of all large retinal vessels, cellophane maculopathy.*

coloured appearance and ill defined margins.

In a small number of patients the birdshot lesions were larger than ¼ DD, were more round than oval, and did not show a radial distribution; however, their appearance was symmetrical.

More exceptionally, a few sharply defined white atrophic spots were seen among the typical birdshot lesions, mostly in the posterior pole (Fig. 3B).

Distribution. The densest concentration of lesions was seen around the optic disc and in the nasal periphery. In many eyes lesions were adjacent to the optic nerve head, giving the disc a typical petaloid appearance (Fig. 4). Sometimes the macular area was involved, but in most patients no flecks were present within the vascular arcades, apart from peripapillary lesions. In some eyes, with only a few or less prominent flecks, they were nearly always located in the inferonasal fundus.

In the majority of cases the lesions showed a well defined pattern radiating from the optic disc towards the periphery. There they often became confluent and formed long yellow-white streaks, following the large choroidal vessels (Fig. 2C).

Another common feature was the tendency of the lesions to progress into large geographic areas of choroidal depigmentation. These areas were most frequently found in the nasal periphery and around the optic disc. In these zones the large choroidal vessels were easily visible and appeared to be enlarged (Fig. 2).

In most eyes depigmentation of the lesions and of the atrophic areas was total and not associated with either pigment migration or hyperpigmentation. In some eyes there were tiny round, dark brown, sharply defined dots scattered over the fundus, unrelated to the lesions or depigmented areas (Fig. 4C).

Fluorescein angiography. In the majority of cases the birdshot spots were not evident in the early stage of angiography, becoming apparent in the venous phase as faint hyperfluorescent flecks which did not increase in intensity in the late phase (Fig. 4B). In fresh cases, however, the spots remained hypofluorescent during the dye transit (Fig. 4E). The lesions adjacent to the optic nerve head and occasionally those in the posterior pole were hypofluorescent (Fig. 4D). In a few eyes sharply circumscribed atrophic white lesions showed an early and bright hyperfluorescence.

Retinal vessels. There was marked narrowing of the retinal arteries in 124 eyes (61%). In most cases this was associated with an irregularity in the calibre of the veins (Fig. 2F). In addition, small flame shaped haemorrhages (Figs. 2F, 3A) were present in 27 of these eyes, mostly in the posterior pole along the large temporal vessels or near the optic disc.

Retinal vascular leakage was a very common finding on fluorescein angiography (Fig. 4E). A

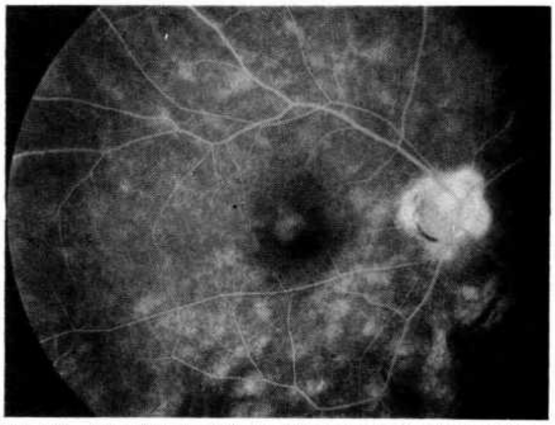


Fig. 4B *Same fundus as in A. Fluoroangiography showing faint hyperfluorescence of the birdshot lesions; slight central macular oedema.*

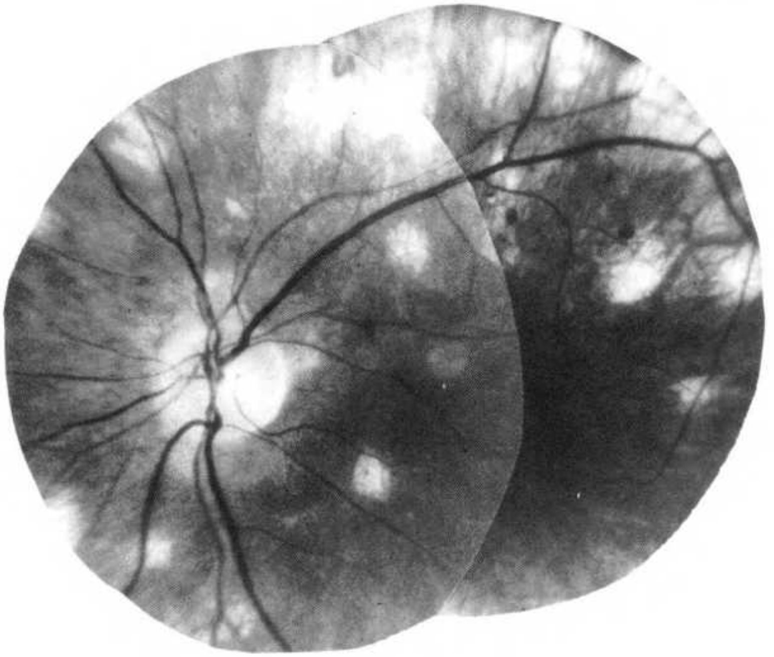


Fig. 4C *Patient aged 55 years (courtesy of A Leys, Leuven). BSCR patient with lesions adjacent to the optic disc (petaloid aspect) and tiny dark dots scattered over the fundus.*

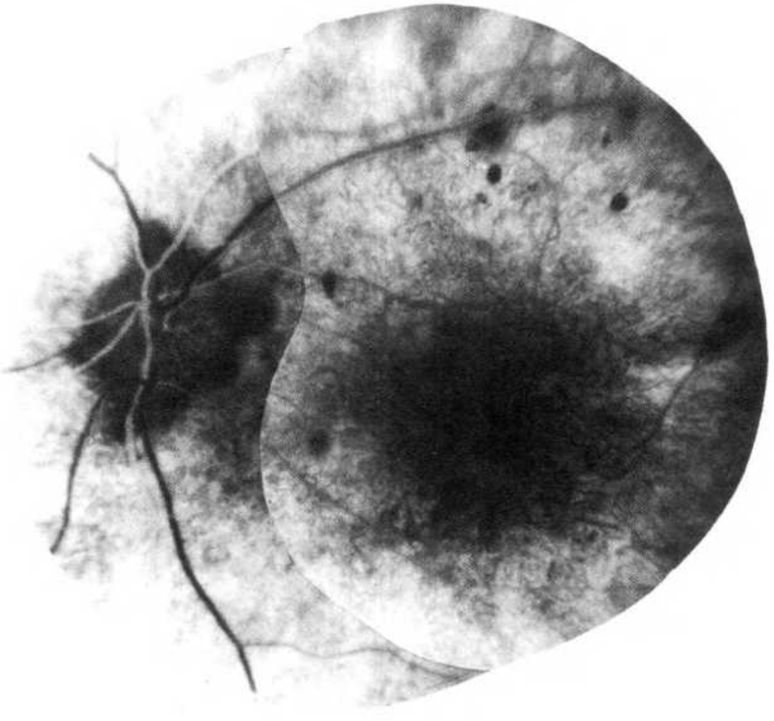


Fig. 4D *Same fundus as C. Fluoroangiogram shows hypofluorescence of atrophic lesions adjacent to the optic disc and of the dark dots.*

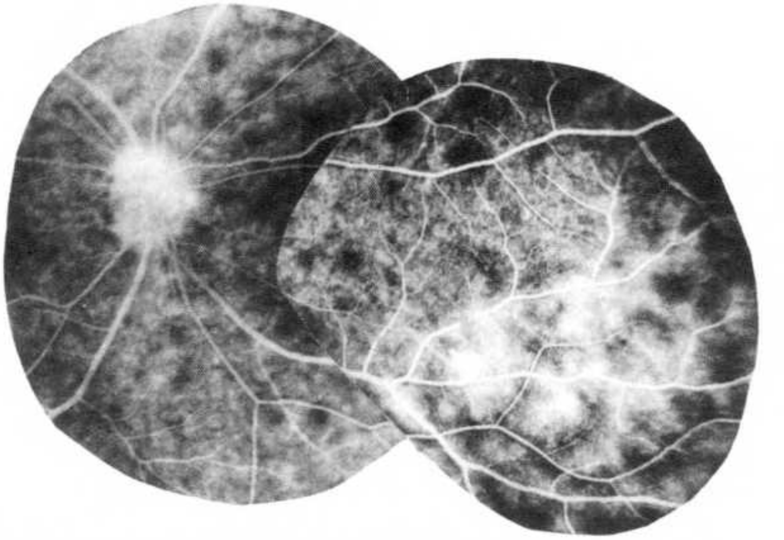


Fig. 4E *Fluoroangiogram of a recently diagnosed case (Gent) of BSCR, showing localised hypofluorescence corresponding with BSCR lesions, capillary dye leakage at the optic disc and in nasal periphery.*

localised staining of the wall of the large retinal veins was seen in 81 eyes (40%). Profuse leakage from the retinal capillaries was the most constant finding, and cystoid macular oedema was present in 127 eyes (62·6%) (Fig. 5A). In none of the patients was retinal capillary closure identified.

Optic disc. Apart from apparent blurred margins, due to lesions adjacent to the optic disc, 77 eyes (38%) showed disc swelling. On fluorescein angiography there was evidence of capillary leakage at the optic nerve head in 38% of all eyes.

ASSOCIATED FINDINGS

These findings were related to complications of the disease (Table 7). The most frequent complications were epiretinal membranes and cellophane maculopathy (Fig. 6A and Fig. 4A), subretinal neovascular membranes (Figs. 6B, D), peripheral retinal and disc neovascularisation (Fig. 5B, Fig. 6E, F), vitreous haemorrhage, and optic atrophy (Fig. 2F). Proliferative retinopathy was particularly common and occurred in the absence of retinal capillary nonperfusion (Fig. 5C, D).

Functional tests

Perimetry, colour vision tests, dark adaptation and electrophysiology studies were performed on only some of the patients (Table 1).

Perimetry was normal in 15 out of 86 eyes, showed peripheral constriction in 30, a central or paracentral scotoma in 28, and an enlarged blind spot in 26 eyes.

The results of colour vision tests were normal in 21 out of 62 eyes, 23 eyes showed only a blue-yellow defect in 23, and 12 eyes showed both blue-yellow and red-green defects.

Dark adaptation was normal in 9 out of 48 eyes tested, borderline in 5, and pathological in 34 eyes (70·8%).

Visually evoked cortical responses were recorded in 60 eyes, 32 of which had abnormal amplitudes (53%), while in another 13 eyes there was an increased latency.

The ERG was normal in 18 out of 84 eyes, in 4 eyes the absence of oscillatory potentials was the only abnormal finding, 14 eyes were borderline, and 46 eyes (54·7%) had an abnormally low ERG. The EOG in 84 eyes showed a subnormal L/D ratio in 60 eyes (Table 8).

HLA typing

Data on HLA typing were available in 48 patients. In 43 the complete HLA A and HLA B loci were screened and in an additional 5 only the HLA A29 was sought. Forty-six out of these 48 BSCR patients (95·8%) carried the antigen HLA A29.

EVOLUTION AND MANAGEMENT

There was no uniformity in the management of the disease in this large group of patients, which reflects their origin from 14 different eye departments. A variety of therapies was used for posterior segment inflammation, including corticosteroids, nonsteroidal anti-inflammatory drugs (indomethacin), immunosuppressive drugs (azathioprine, cyclophosphamide, cyclosporin A), and a variety of antibiotics.

In many cases the indication for treatment was not clear. Owing to different criteria for management of the disease it was difficult to evaluate the influence of therapy on the visual outcome. The data on a group of 27 patients with a follow-up of five years or more

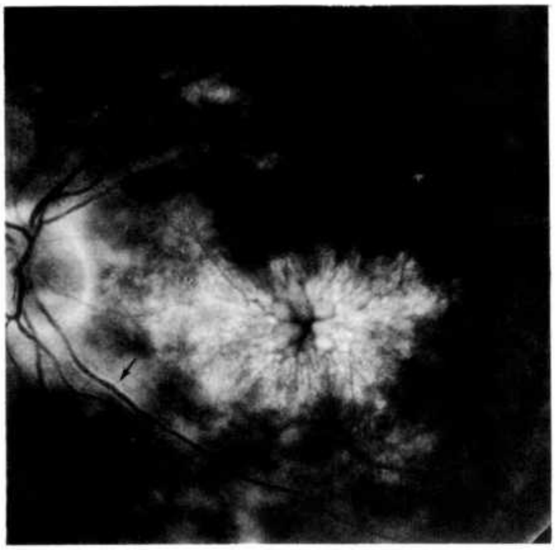


Fig. 5A *Patient aged 68 years (Gent). BSCR with severe cystoid macular oedema. Note also hyperfluorescence of the venous vessel wall (arrow).*

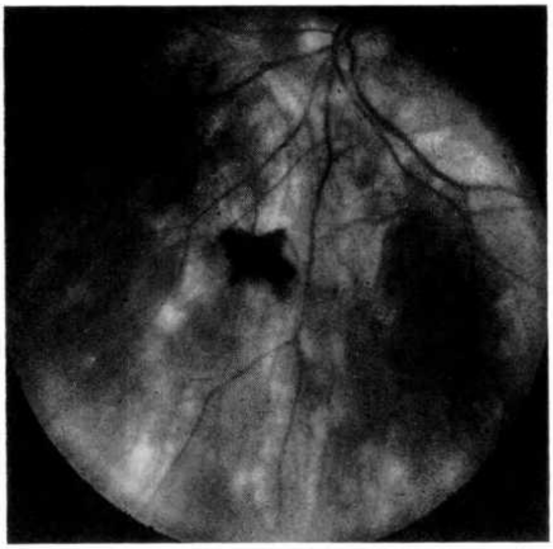


Fig. 5C *Patient aged 55 years (Gent). BSCR with irregular calibre of vessels and a preretinal haemorrhage.*

did not clearly indicate whether steroids and other anti-inflammatory and immunosuppressive drugs were beneficial in BSCR (Table 9).

Argon laser photocoagulation was applied to 17 eyes for treatment of subretinal neovascular membranes (7 eyes), vitreous haemorrhage (4 eyes), macular oedema (3 eyes), and peripheral retinal breaks or peripheral degeneration (3 eyes).

The review period for 62 patients ranged from one month to 13 years. After an evolution of five years or more half of the eyes have maintained a visual acuity of 6/18 or better (Table 10). Loss of visual acuity was

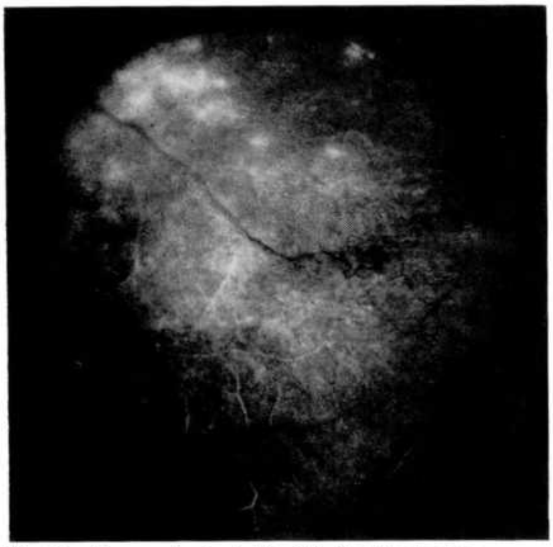


Fig. 5B *Same patient as in Fig. 2A, B with relapsing vitreous haemorrhage in right eye. After clearing of the haemorrhage a teleangiectatic lesion is seen in the temporal periphery.*

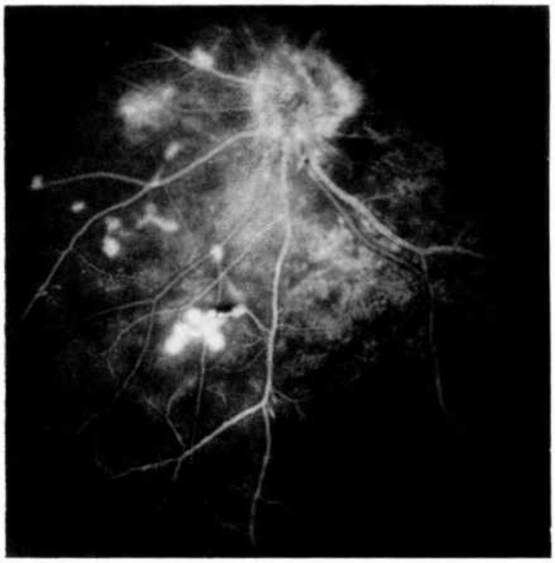


Fig. 5D *Same fundus as 5C. Fluoroangiogram shows multiple sites of retinal neovascularisation and widespread capillary dilatation, but no evidence of capillary closure.*

Table 7 *Complications associated with BSCR*

Total number of eyes with BSCR	203
Epiretinal membrane	20
Retinal neovascularisation	15
Vitreous haemorrhage	5
Subretinal neovascular membrane	
Parapapillary	4
Macular	8
Optic atrophy	7

Table 8 *EOG in 84 eyes with BSCR*

L/D ratio	*Number of eyes*
171–200%	22
151–170%	11
131–150%	23
111–130%	15
<110%	11

due to cystoid macular oedema, epiretinal membrane in the macula, macular hole, subretinal neovascular membrane, macular scar, and cataract. Vitreous haemorrhage and vitreous floaters were important causes of visual loss in the initial stages of the disease but did not contribute to the final visual outcome in the group of patients with a minimum follow-up period of five years.

Improvement of visual acuity was seen in 13 eyes as a result of clearing of vitreous haemorrhage (3 eyes), removal of cataract (3 eyes), laser photocoagulation of subretinal new vessels (2 eyes), and regression of inflammatory signs (5 eyes).

A few eyes showed a remarkable evolution in the appearance of the hypopigmented spots (Fig. 3). Five patients initially had no clear evidence of birdshot spots in the fundus when they presented with papillitis, retinal vasculitis, and varying degrees of vitritis in both eyes. The typical fundus picture of BSCR did not appear until several years later, mostly when the signs of acute inflammation had resolved.

Discussion

MEDICAL AND OCULAR ASSOCIATIONS

The apparently high prevalence of vascular diseases might indicate that BSCR is associated with a general vascular disorder. No other systemic diseases seem to be relevant to the disease. Because Gass[2] stressed the association of BSCR with vitiligo, this was especially sought; however, only one out of 102 patients was known to have depigmentation of the skin and only after exposure to the sun. Moreover, Wagoner *et al.*,[18] on examination of 223 patients with vitiligo, found evidence of BSCR in only one. Since multifocal choroidal disease is known to occur in sarcoidosis,[5, 19] at least 38 patients were fully investigated by

Table 9 *Visual outcome in 27 BSCR patients after five years or more*

Patient no	*Initial VA*	*Final VA*	*Cause of visual loss*	*Follow-up (years)*	*Treatment*
1	6/18 6/24	6/24 CF	CME CME	8	Steroids, laser LE
2	6/12 6/12	6/6 6/6	CME CME	10	Steroids
3	CF CF	CF CF	Macular scar Subretinal neovasc	5	Laser LE
4	6/6 6/7·5	CF CF	CME CME	8	Steroids, cyclophosphamide, cyclosporin A+
5	6/12 6/12	6/60 6/60	CME CME	6	Steroids
6	6/18 6/6	CF 6/12	CME CME	6	Steroids, cyclosporin A
7	6/12 6/6	6/9 6/6	Vitreous opacities	9	Steroids
8	6/6 6/5	6/60 6/9	CME+pucker CME+cellophane	5	Steroids
9	6/9 6/12	6/12 6/9	CME CME	5	Indomethacin
10	6/12 CF	6/12 CF	CME Cataract+retinal detachment	5	Steroids
11	6/12 6/9	6/18 6/60	PE alteration Subretinal neovasc	6	Sphiramycin, steroids, Laser LE
12	6/12 CF	6/12 CF	CME CME	6	
13	6/6 6/60	6/6 6/60	CME CME	11	Steroids, laser macula LE
14	6/9 6/9	6/60 6/24	CME+vitreous haemorrh CME	9	Steroids, azathioprine
15	6/9 6/9	HM 6/60	CME CME	13	Steroids, azathioprine
16	6/18 6/12	6/60 6/36	CME+cataract CME+cataract	5	Steroids, IOL RE
17	CF CF	CF LP	Optic atrophy Optic atrophy	5	None
18	6/9 6/6	6/9 6/9	CME CME+cellophane	5	Steroids
19	6/9 HM	6/9 HM	Secondary glaucoma Secondary glaucoma	5	Trabeculectomy RE+LE
20	6/18 6/7 5	6/5 6/6		7	Steroids, systemic+topical
21	6/24 6/24	6/24 6/18	CME CME	10	Steroids
22	6/6 6/7 5	6/6 6/6		11	Steroids retrobulbar
23	6/4 6/4	6/4 6/4		9	Steroids topical
24	6/60 6/12	6/60 6/12	CME CME	8	Steroids, azathioprine, indomethacin
25	6/6 6/6	6/6 6/12		5	Steroids
26	6/7 5 6/18	6/12 6/18	PE alterations Subretinal neovasc	6	Steroids, laser subretinal neovasc
27	6/36 6/24	CF CF	CME CME	6	Steroids, laser LE

CME=cystoid macular oedema CF=counting fingers.

Table 10 *Visual acuity at last control (numbers of eyes)*

Visual acuity	*Follow-up period*			
	1 year	*2 years*	*5 years*	*8 years*
6/7·5+	21	17	3	8
6/18–6/9	23	25	13	3
6/60–6/24	14	12	6	7
<6/60	10	3	10	4

means of chest *x*-ray, full blood counts, biochemical tests including calcium and angiotensin-converting enzyme, Kveim test, and sometimes biopsy of skin lesions. However, in only one was evidence of sarcoidosis found, one other case of BSCR associated with sarcoidosis has been reported in Japan.[19]

There was a particularly high incidence of open angle glaucoma (15 eyes, 19%) not associated with pigment dispersion in the anterior chamber and without evidence of elevated venous episcleral pressure.

Two of the 79 patients with available ocular history had a rhegmatogenous retinal detachment, and another patient had laser treatment for a peripheral retinal hole with operculum. The occurrence of rhegmatogenous retinal detachment in BSCR has been recorded[1 4 10 11] and is a recognised complication of uveitis.[20] Rhegmatogenous retinal detachment may complicate BSCR due to alterations and shrinkage. The finding of minimal involvement of the anterior segment is consistent with the other clinical reports on BSCR, as is the case with the high percentage of vitreous opacities.

In general, the medical history and examinations were not helpful in establishing an aetiological factor for BSCR.

FUNDUS CHANGES

The ophthalmoscopic and fluorescein-angiographic findings of the birdshot lesions, retinal vasculopathy, and most of the complications have been previously reported.

The depigmented choroidal lesions are the most prominent feature of BSCR. Several suggestions have been made regarding the pathogenesis of these lesions, depending on speculations as to their nature and on their level in the eye. According to Ryan and Maumenee[1] 'the depigmented spots may be related to previous accumulation of fluid or to inflammatory foci in the choroid or in the retinal pigment epithelium'. Gass,[2] however, finds the patches 'unlike most other infiltrative or atrophic hypopigmented fundus lesions' because they are not elevated as they are with a nodular inflammatory cellular infiltrate, nor are they depressed as in the case of atrophy of the choroid and retina. He suggests that they are 'caused by focal depigmentation of the choroidal melanocytes' and compares the lesions with vitiligo of the skin We could not establish a relation with vitiligo in our patients. Moreover, the birdshot lesions have a distribution which does not correspond with the diffuse presence of the melanocytes in the choroid.

Several findings suggest that the birdshot lesions are located in the outer choroid and are associated with the large choroidal vessels. On many occasions large choroidal vessels are clearly seen to cross over the lesions (Fig. 2C). The birdshot lesions show a radial arrangement round the optic disc; this distribution corresponds most with the pattern of the large choroidal vessels and more specifically the choroidal veins. Most eyes showed macular sparing by the birdshot lesions, an area which in most people is relatively free of large choroidal veins. However, the lack of lesions in the central fundus is not a constant feature, and one case has been reported in which the macula was the most affected site.[14] Very often the more peripheral lesions are confluent and form elongated yellow-white streaks parallel to the choroidal vessels, suggestive of vascular sheathing. Their predominant occurrence nasally inferior to the optic disc and the development of confluent lesions in the inferior nasal quadrant have also been reported by other authors.[8 14] The large size and high density of both choroidal veins and lesions at this site may be significant. The deep location of the lesions would explain their indistinct appearance and the lack of secondary retinal pigment-epithelial reaction or disturbance even in longstanding cases. The mild late phase hyperfluorescence of the birdshot lesions is in accordance with a deep seated inflammatory focus which gradually accumulates fluorescein.

Retinal vasculopathy was a major feature of BSCR in this group of 203 eyes, manifest as cystoid macular oedema in 127 eyes (62·6%) and perivascular leakage in 81 eyes (40%). In several eyes the retinal vasculitis associated with vitreous cells and papillitis was the presenting sign of the disease.

Retinal neovascularisation occurred in 15 eyes in the absence of retinal capillary closure, making it unlikely that the growth was in response to

Fig. 6 *Complications in birdshot chorioretinopathy.* A: *Patient aged 56 years (Gent) Epiretinal membrane superior to optic disc (arrows).* B: *Patient aged 58 years (courtesy of P Amalric, Albi). BSCR with juxtapapillary subretinal neovascularisation* C: *Patient aged 52 years (courtesy of P Amalric, Albi). Left eye in 1981 note white birdshot lesion under the macula* D. *Same fundus as C in 1983. subretinal neovascularisation has developed at the site of the birdshot lesion.* E. *Patient aged 44 years (courtesy of J Shilling, London). BSCR with prepapillary neovascularization (July 1978)* F: *Same fundus as E Peripheral retinal neovascularisation.*

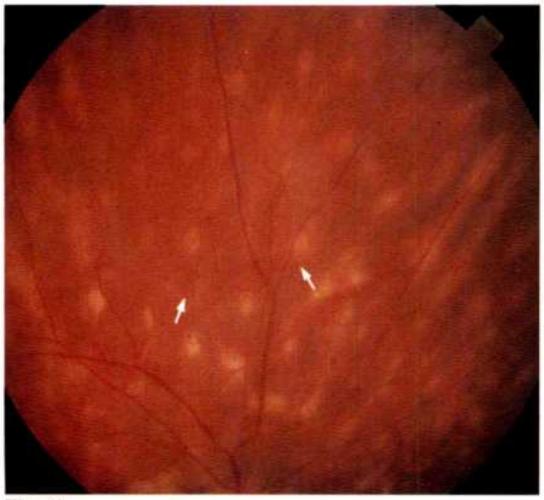
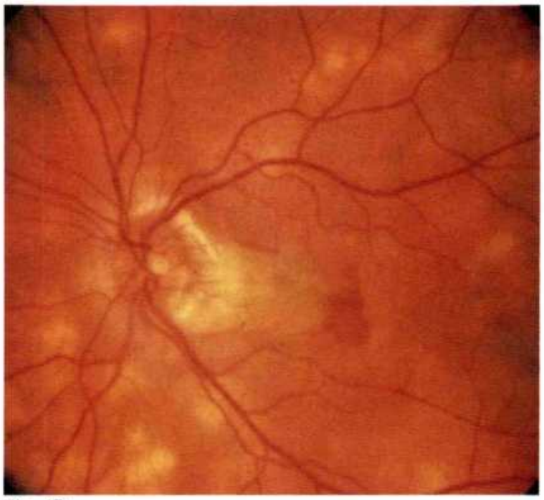


Fig. 6A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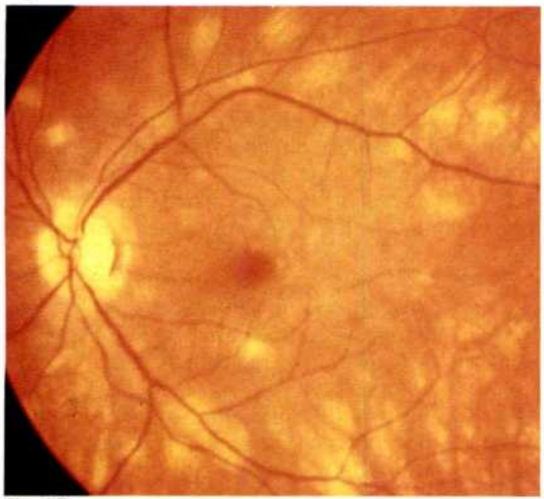
Fig. 6C

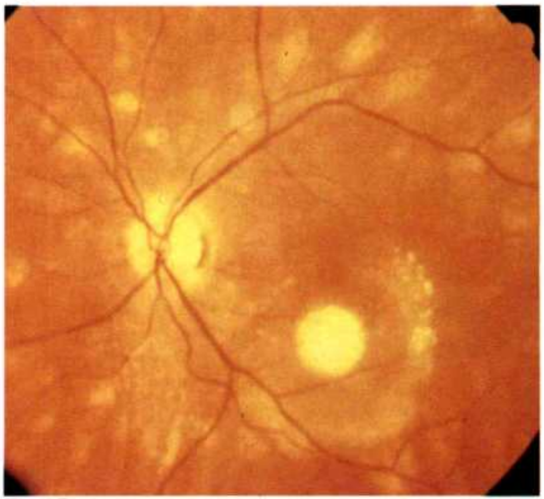
Fig. 6D

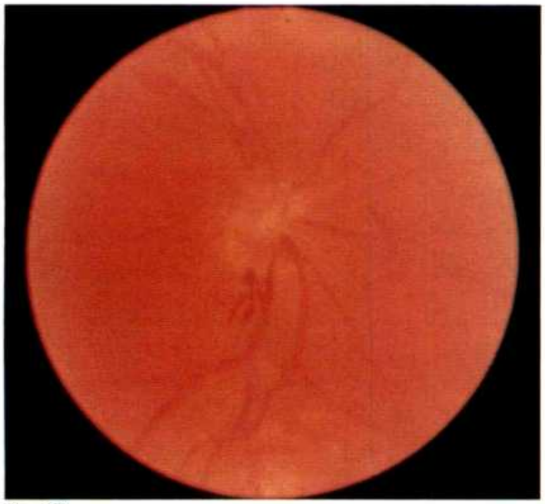
Fig. 6E

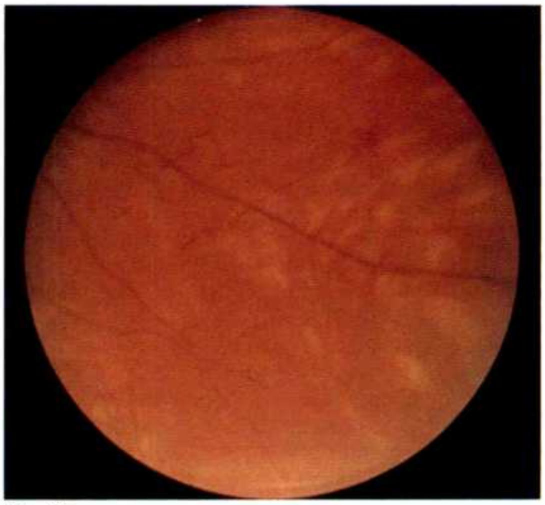
Fig. 6F

ischaemia. Recurrent vitreous haemorrhages and the presence of small preretinal neovascular tufts have not yet been described in BSCR. Felder and Brockhurst[21] reported retinal neovascularisation in patients with posterior uveitis in the absence of capillary non-perfusion, and Henkind[22] considered that inflammation locally in the retinal vascular bed is a sufficient stimulus for the growth of new vessels, though he found these were more readily induced at the disc than in the retinal vessels. In our BSCR patients only two eyes showed neovascularisation at the edge of the optic nerve head and 13 eyes showed peripheral retinal neovascularisation.

The observation of subretinal neovascularisation in 12 eyes with BSCR is in accordance with the observation of Soubrane *et al.*,[8] who reported on three BSCR patients with juxtapapillary subretinal neovascularisation, and Brucker *et al.*,[9] who observed macular subretinal choroidal neovascularisation in four eyes of two patients with BSCR. In two eyes of our series there appeared to be a relationship between a birdshot lesion and the development of a subretinal neovascular membrane (Fig. 6C, D). This is not surprising, as new vessels may arise from atrophic chorioretinal scars, irrespective of their origin.

CONCLUSIONS

1. The fundus appearance of BSCR shows a high degree of uniformity and is now well defined, as has been demonstrated in a large group of patients. It shows a characteristic pattern of multiple small depigmented flecks, radiating from the margins of the optic nerve head towards the periphery. It is bilateral and in most cases symmetrical.

The condition is further characterised by the presence of various inflammatory signs, mainly in the posterior segment and only very seldom in the anterior segment. Some patients may initially present with a mild to severe vitritis associated with disc oedema, retinal vasculitis, and cystoid macular oedema before the flecks become apparent; as the choroidal lesions appear the retinal and vitreous changes often regress. Other patients present at their first visit with the typical spotted retina with only minimal involvement of the vitreous and the retinal vessels. In these cases a low grade inflammation may also have been present for some time, giving rise to a long history of floaters or in some patients not causing ocular complaints. The sequelae of previous inflammation, such as optic atrophy, chronic cystoid macular oedema, epiretinal membranes, peripheral retinal and disc neovascularisation, and subretinal neovascular membranes are common. It would appear that BSCR may begin with simultaneous inflammatory reactions in the vitreous, the retina, and the choroid, and that after a period of more or less active inflammation the condition tends to stabilise.

The disease is rare, as only 102 cases of typical BSCR were collected in 14 major European eye clinics during the period 1980–6, and it affects people in middle life without predilection for sex.

2. From the various clinical manifestations it is now possible to consider diagnostic criteria. The major criterion is the characteristic spotted fundus appearance associated with evidence of posterior segment inflammation and/or evidence of known complications of the disease.

Ranged according to their frequency, the ophthalmoscopic signs are vitritis (83%), cystoid macular oedema (62·6%), arteriolar narrowing and irregularity of veins (61%), retinal vasculitis (40%), disc oedema (38%), cellophane-like maculopathy (10%), retinal neovascularisation (7·5%), subretinal neovascularisation and macular scar (6%), optic atrophy (3·5%).

The minimal criteria necessary for the diagnosis of BSCR could be formulated as bilateral presence of typical birdshot spots in the fundus and two or more signs from the preceding list. A further important criterion may be the association with the antigen HLA A29.

3. The aetiology remains speculative. There appears to be no specific link with any systemic disease, although arterial hypertension and vascular occlusive disease occurs rather frequently in this group of patients.

The specificity of the ophthalmoscopic appearance of BSCR, the constancy of its behaviour, and its very high association with HLA A29 together suggest that BSCR is a single nosological entity. There is no evidence of a single cause, and it is possible that the disorder represents a specific response to a variety of pathogenetic agents.

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Reflow of obstructed capillaries in the maculae of humans with diabetic retinopathy, observed by fluorescein angiography

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SUMMARY As diabetic retinopathy progresses, the non-perfused area in the retina gradually enlarges as the capillaries are obstructed. To elucidate the process of capillary obstruction we examined macular capillaries in 104 diabetics, using fluorescein angiography. The follow-up period was three to eight years. We found that some capillaries in the macula were obstructed, then became unobstructed. Reflow of blood into the macula after the obstruction was observed in nine patients (8·7%). The time between obstruction and reflow varied from two months to four years. There were four cases of simple, three of preproliferative, and two of proliferative retinopathy. Reflow in the capillaries was confirmed as occurring at the same position and in vessels with the same diameter as seen before the obstruction. There was no leakage of the fluorescein dye from the capillary where reflow took place. We tentatively conclude that one of the causes of this phenomenon is a functional obstruction.

It is generally accepted that diabetic retinopathy is a form of microangiopathy. As the retinopathy progresses, the non-perfused area in the retina gradually enlarges as a result of obstruction of the capillaries.

Although several ophthalmologists reported this phenomenon, each report was of one case and the state of the capillaries before the obstruction was not described.[1-4] Almost all reported that this phenomenon occurred after photocoagulation. We therefore examined the occurrence rate of the reflow of the obstructed capillaries, the type of capillary reflow, and the possible relation to photocoagulation.

Subjects and methods

Fluorescein angiography was carried out from 1977 to 1985 on 104 eyes of 104 diabetics aged 16 to 78 years. All were treated by diabetologists and the follow-up was for three to eight years. Thirty were cases of insulin-dependent diabetes mellitus (IDDM) and 74 of non-insulin-dependent diabetes mellitus (NIDDM). Diabetics without retinopathy, determined by ophthalmoscopy, numbered 22. In 58 cases there was a simple retinopathy, 18 had a preproliferative retinopathy, and six a proliferative retinopathy.

All patients were examined by ophthalmoscopy after the pupil had been dilated with 10% phenylephrine and 0·5% cyclopentolate. Fluorescein fundus angiography and colour photography were carried out periodically, the frequency depending on the severity of the diabetic retinopathy. 5 ml of 10% sodium fluorescein was given intravenously.

We examined coagulation and platelet aggregation at the time of occlusion, and adenosine-5'-diphosphate (ADP) and coagulation were examined at the time of occlusion and after reflow in patient 1 and after reflow in eight patients.

Results

Reflow of blood into the macular capillary bed after the obstruction occurred in nine of the 104 diabetics (8·7%). Table 1 is a summary of data on nine with a reflow in the obstructed capillaries. Five were cases of IDDM and four of NIDDM. The ages of the patients at the time of reflow ranged from 19 to 53

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Table 1 *Summary of nine cases*

Patients	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Age	46	48	30	53	19	35	43	34	46
Sex	Female	Female	Female	Female	Female	Male	Male	Male	Male
Type of diabetes	NIDDM	NIDDM	IDDM	NIDDM	IDDM	IDDM	IDDM	IDDM	NIDDM
Duration of diabetes (yr)	5	10	11	11	12	13	16	17	22
Photocoagulation	–	–	–	–	–	–	+	–	+
Control of blood sugar	Poor	Poor	Poor	Poor	Fair	Poor	Poor	Poor	Poor
Other complications	—	—	—	—	—	—	Np	Np, Nr	—
Visual acuity									
before occlusion	0·9	0·1	0·8	0·9	0·8	1·0	0·8	1·0	0·4
after occlusion	0·7	0·1	0·8	0·7	1·2	0·6	0·7	0·6	0·7
Retinopathy									
before occlusion	S	PP	S	S	S	S	PP	PP	P
after occlusion	PP	PP	S	S	S	S	PP	P	P

Np: nephropathy. Nr: neuropathy. S: simple retinopathy. PP: preproliferative retinopathy. P: proliferative retinopathy.

years. There were four men and five women. The duration of diabetes was over 10 years in all cases except one, in which it was 5 years. Blood sugar control was poor except for one case, where it was fair; however, there was no history of hypoglycaemic attack. Visual acuity ranged from 0·1 to 1·0 at the time of occlusion and after reflow in nine cases. Visual acuity worsened in five, improved in two, and was unchanged in two. One had nephropathy, and another nephropathy and neuropathy. Photocoagulation was performed on 32 of the 104 diabetics and on two of the nine cases with reflow.

Table 2 shows data on the coagulation of nine patients. Data after reflow showed increased platelet coagulation activity. Data on patient 1 showed an increase in platelet coagulation activity both during occlusion and after reflow of the capillary.

Case reports

CASE 6

A 35-year-old man (Figs. 1–3) had had IDDM for seven years. His right eye showed a simple retinopathy. Fig. 1 shows colour fundus photographs (in black-and-white) and fig. 2 fluorescein angiographs, at the late stage. The upper photographs 'a' of Figs. 1 and 2 indicate the time before obstruction, the middle photographs 'b' indicate the time of obstruction, and the lower ones 'c' the time after the reflow. These photographs demonstrate a gradual progression of simple retinopathy. Fig. 3 shows enlarged angiographs of the macular area in this patient. The capillary indicated by the arrow is the normal angiogram in photograph 'a'.

Two years and eight months later that capillary was absent in photograph 'b'. This occluded capillary was not demonstrated from the early capillary phase to the late phase. However, two years and 10 months after the time of 'b' there was a reflow in photograph 'c' at the same position and with the same diameter as in photograph 'a'. There was no leakage of the fluorescein dye from the capillary, as indicated by the arrow. Damage of other capillaries of the surrounding fovea progressed from the time of 'a' to the time of 'b'.

CASE 8

A 34-year-old man (Figs. 4–6) had had IDDM for 12 years. His right eye showed a preproliferative retinopathy at the time of 'a' and progressed to proliferative

Table 2 *Coagulation*

Patients	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*Control*
Platelet aggregation										
Factor IV (ng/ml)										≤20 μg/l
after reflow	30	100 ↑	63	100 ↑	85	30	50	78	80	
β-thromboglobulin (ng/ml)										≤50 μg/l
after reflow	110	200 ↑	150	170	170	110	99	150	200 ↑	
ADP (%)										≤56% (2 μmol)
before occlusion	61	—	—	—	—	—	—	—	—	
after reflow	61	46	64	59	48	72	52	64	—	
Collagen (%)										≤66% (1 mg/l)
before occlusion	97	—	—	—	—	—	—	—	—	
after reflow	97	64	79	89	58	86	48	78	—	

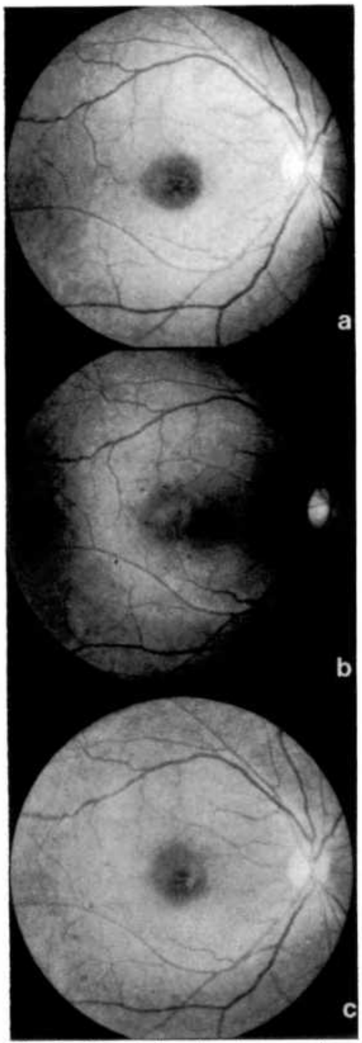


Fig. 1 *Case 6. Fundus photographs of a 35-year-old man who had had IDDM for seven years. His right eye showed a simple retinopathy. Figs. 1a, 2a, 3a were taken at the time before obstruction, Figs. 1b, 2b, 3b at the time of obstruction, and Figs. 1c, 2c, 3c after the reflow.*

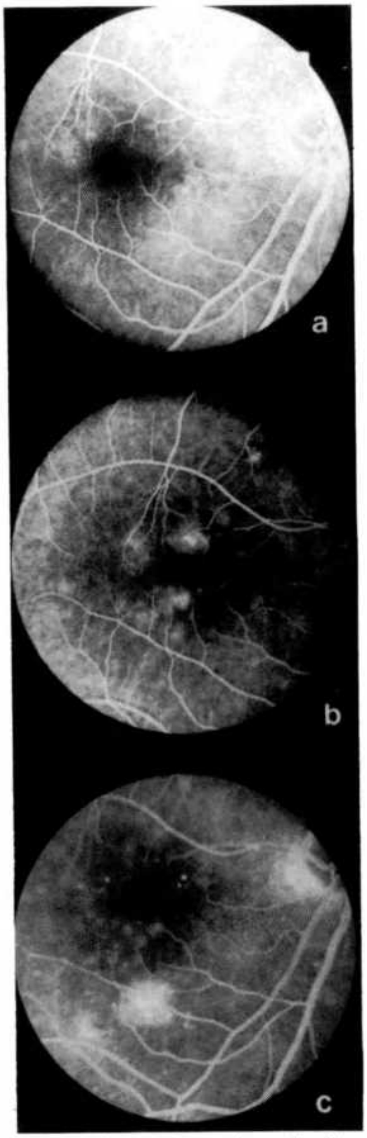


Fig. 2 *Fluorescein angiographs of Fig. 1 at the late stage. A gradual progression in simple retinopathy is evident.*

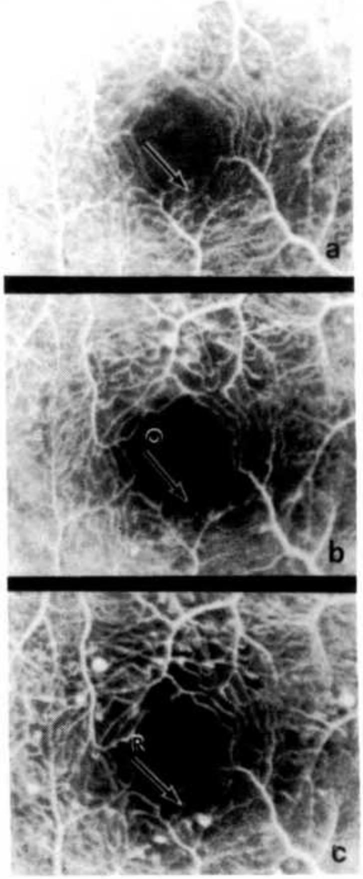
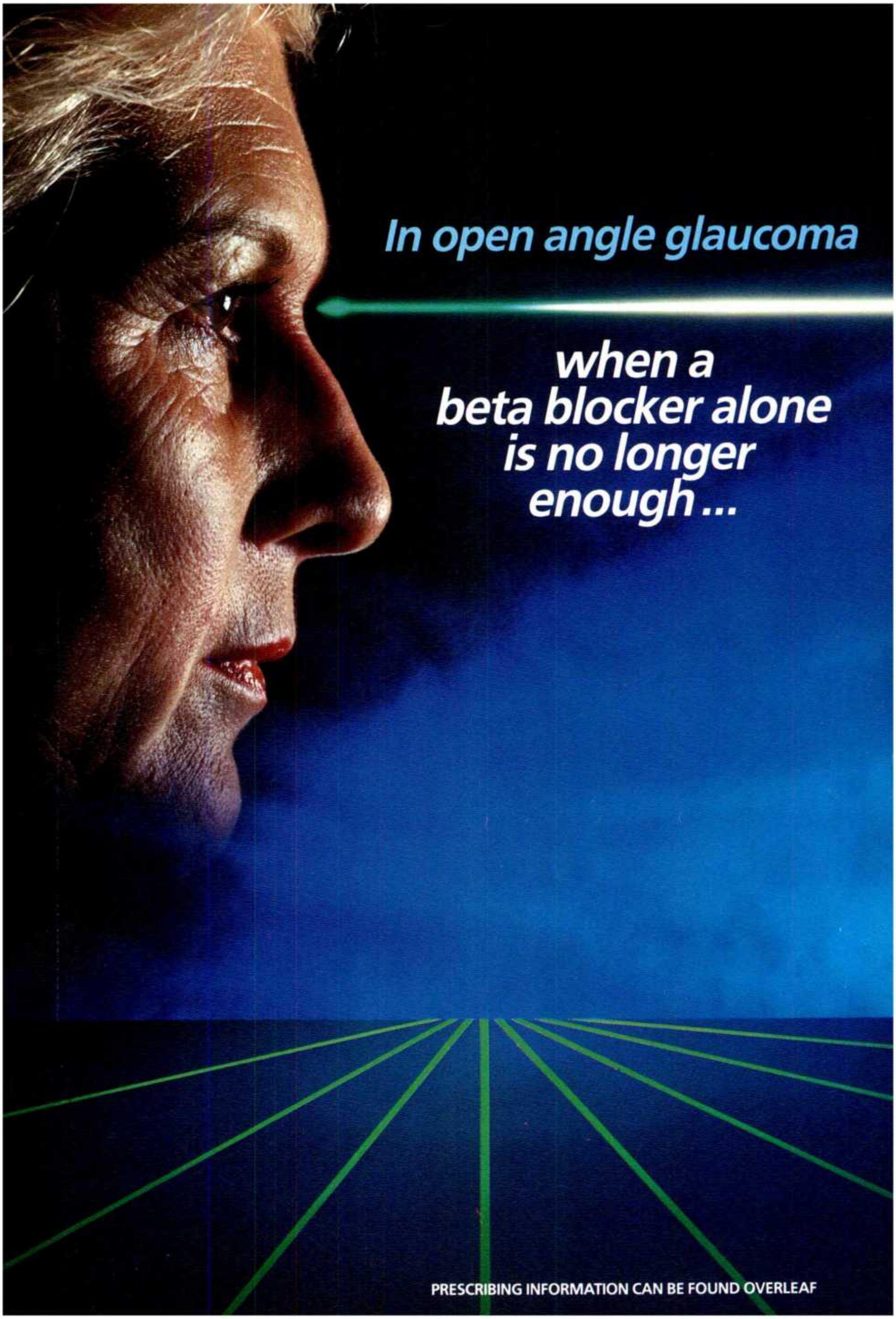


Fig. 3 *Enlarged angiographs of the macular area of the case 6. The capillary indicated by the arrow shows the normal angiogram in photograph* a. *Two years and eight months later this same capillary cannot be seen in photograph* b. *However, two years and 10 months after the time of* b *there is a reflow, in photograph* c, *at the same position and with the same diameter as seen in photograph* a. *There is no leakage of the fluorescein dye, as indicated by the arrow.*

retinopathy at the time of 'c' (Figs. 4–5). Fig. 6 shows enlarged angiographs of the macular area. The capillary indicated by the arrow is the normal angiogram in photograph 'a'. This same capillary in photograph 'b' is not evident four years and 10 months later. This occluded capillary was not visible from the early capillary phase to the late phase. However, three months after the time of 'b' there was evidence of a reflow in photograph 'c', at the same position and with the same diameter as seen in photograph 'a'. There was no leakage of the fluorescein dye from the capillary, as indicated by the arrow.

CASE 2

A 48-year-old woman (Figs. 7–9) had had NIDDM for nine years. Her right eye showed a preproliferative retinopathy and this state gradually worsened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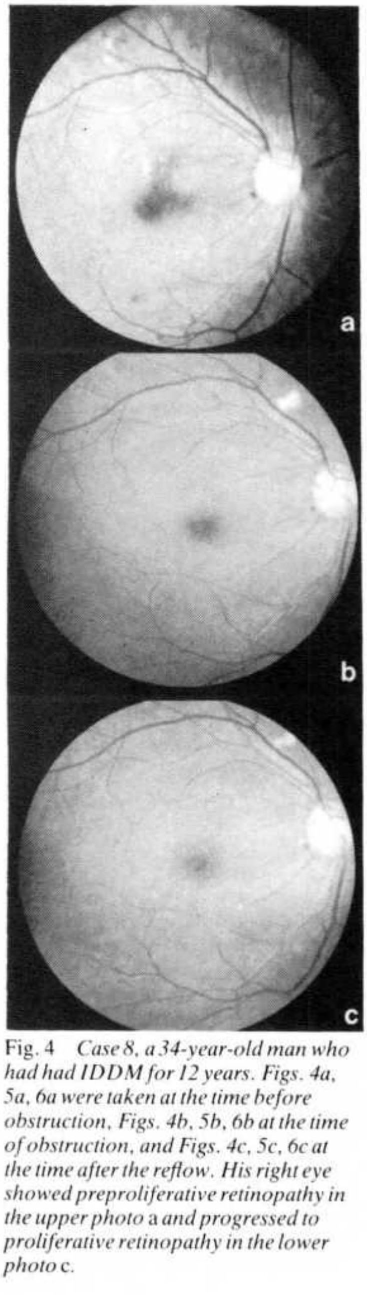

Fig. 4 *Case 8, a 34-year-old man who had had IDDM for 12 years. Figs. 4a, 5a, 6a were taken at the time before obstruction, Figs. 4b, 5b, 6b at the time of obstruction, and Figs. 4c, 5c, 6c at the time after the reflow. His right eye showed preproliferative retinopathy in the upper photo* a *and progressed to proliferative retinopathy in the lower photo* c.

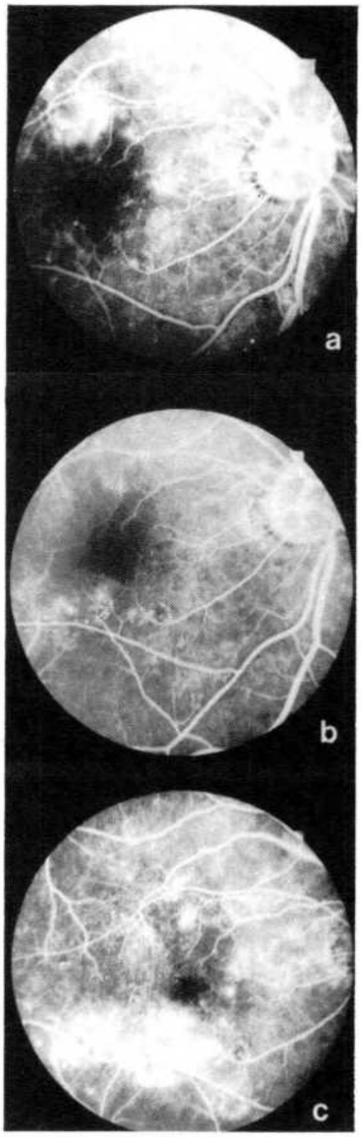

Fig. 5 *Fluorescein angiographs of Fig. 4 at the late stage. There is mild leakage and progression of retinopathy in the macular area.*

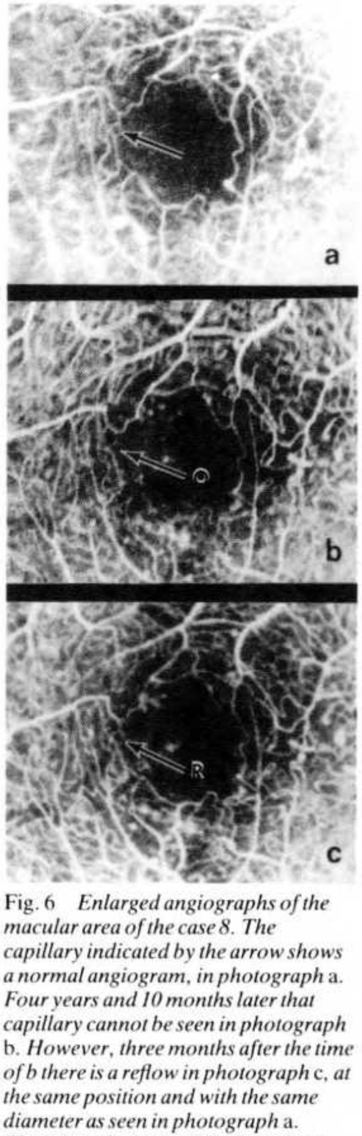

Fig. 6 *Enlarged angiographs of the macular area of the case 8. The capillary indicated by the arrow shows a normal angiogram, in photograph* a. *Four years and 10 months later that capillary cannot be seen in photograph* b. *However, three months after the time of b there is a reflow in photograph* c, *at the same position and with the same diameter as seen in photograph* a. *There is no leakage of the fluorescein dye, as indicated by the arrow.*

(Figs. 7–8). Fig. 9 shows enlarged photographs of the macular area. The capillary indicated by the arrow is the normal angiogram in photograph 'a'. Three years and eight months later that capillary was absent in photograph 'b'. This occluded capillary was not angiographed at the late stage. However, two months after the time of 'b' the capillary was visible in photograph 'c', at the same position and with the same diameter as seen in photograph 'a'. There was no leakage from the capillary, as indicated by the arrow.

Discussion

It is generally accepted that, in vasculo-occlusive disease such as diabetic retinopathy, as the retino-

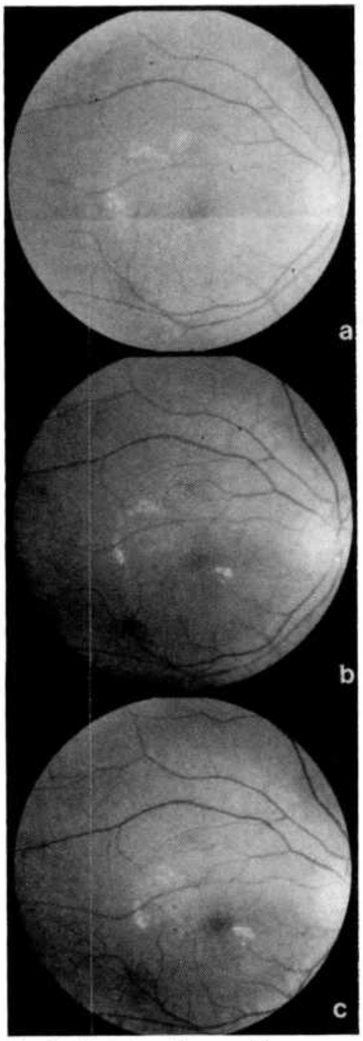

Fig. 7 *Case 2, a 48-year-old woman who had had NIDDM for nine years. Figs. 7a, 8a, 9a were taken at the time before obstruction, Figs. 7b, 8b, 9b at the time of obstruction, and Figs. 7c, 8c, 9c at the time after the reflow. Her right eye showed preproliferative retinopathy in the upper photo* a, *and the retinopathy gradually progressed in the lower photo* c.

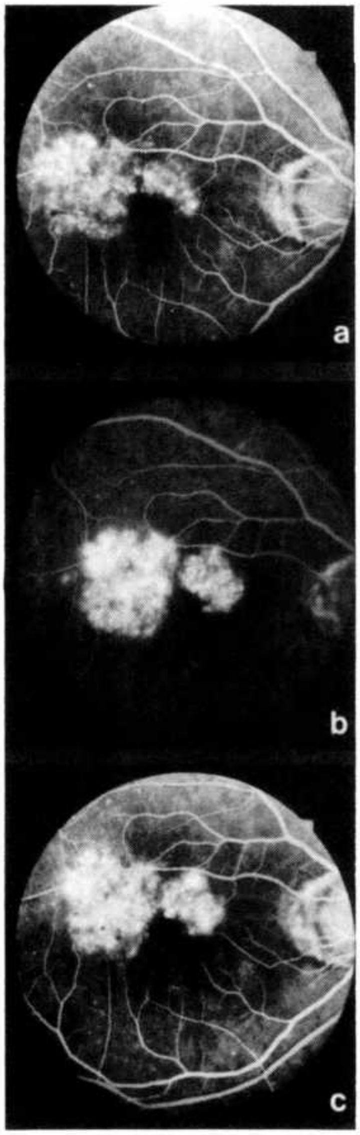

Fig. 8 *Fluorescein angiographs of Fig. 7 at the late stage. There is extensive leakage and progression of retinopathy in the macular area.*

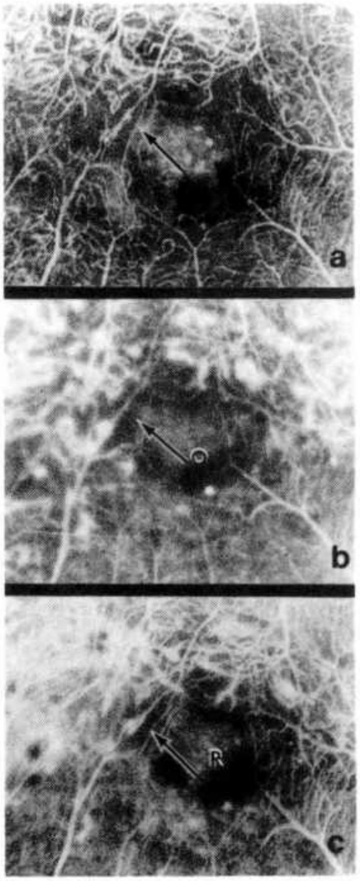

Fig. 9 *Enlarged angiographs of macular area in the case 2. The capillary indicated by the arrow shows the normal angiogram in photograph* a. *Three years and eight months later that capillary cannot be seen in photograph* b. *However, two months after the time of* b *there is a reflow in photograph* c, *at the same position and with the same diameter as seen in photograph* a. *There is no leakage of the fluorescein dye, indicated by the arrow.*

pathy progresses the non-perfused area in the retina gradually enlarges owing to obstruction of the capillaries. On the other hand there are reports on the reflow of blood into the capillary after obstruction in cases of retinal vein occlusion,[6] Takayasu's disease,[7] sickle cell retinopathy,[8] and diabetic retinopathy.[1-5] It was reported that recanalisation occurred after photocoagulation, and capillaries were not visible before the obstruction.

It is necessary to distinguish a capillary with a reflow from a new vessel. We examined and followed up macular capillaries of diabetics, using fluorescein angiography, the objective being to elucidate the process of capillary obstruction. We observed capillaries before the obstruction, at the time of obstruction, and after the reflow of blood. These capillaries are at the same position and had the same diameter as before the obstruction. There was no leakage of fluorescein dye from the capillary. Therefore these capillaries are not new vessels and the obstructions of the capillaries are probably functional, not organic. The reflow of blood was not observed in cases of early diabetic retinopathy and cases without retinopathy by ophthalmoscopy and fluorescein angiography.[9]

There is well substantiated evidence that patients with diabetes and also experimental diabetic rats have abnormalities of platelet aggregation.[10,11] The presence of a significant delay of systemic and intraocular circulation in diabetics, determined by fluorescein angiography, has been reported.[12] Coagulation and platelet aggregation in our patients were accelerated not only at the time of occlusion but also after reflow, and in all of them the retinopathy progressed. This evidence indicates that capillary flow in diabetics with progressive retinopathy is sluggish or repeatedly ceases under conditions of acceleration of coagulation and platelet aggregation. One cause of this phenomenon is functional obstruction.

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Effects of intensified insulin treatment on retinal vessels in diabetic patients

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SUMMARY Forty-five diabetic patients were randomly assigned to treatment with continuous subcutaneous insulin infusion (CSII), multiple injections (MI), and conventional insulin treatment (CIT). They were prospectively followed up for one year. A computerised scanning microdensitometer was applied on fundus photographs of retinal vessels, and we studied changes in calibres of the blood column (W_0) and in width (W_r/W_0) and intensity (I_r) of the central 'light reflex'. After six months of improved metabolic control the I_r was reduced in both MI and CSII cases compared with CIT cases ($p<0{\cdot}01$), indicating haemorrheological changes in the retinas. Within these six months cotton-wool spots appeared in half the patients ($n=15$) on CSII and MI, but not in CIT patients. Subjects who developed cotton-wool spots, compared with those who did not, had greater intensities of reflection and larger calibres of vessels at the start of the study ($p<0{\cdot}01$). On intensifying the treatment they were characterised by a larger fall in hemoglobin A_1 ($p<0{\cdot}01$) and by a larger decrease in I_r on arteries ($p<0{\cdot}05$) and veins ($p<0{\cdot}01$). The behaviour of the retinal circulation is different in patients developing transient ischaemic lesions on intensified insulin treatment from its behaviour in those who do not.

A worsening of diabetic retinopathy has been observed when intensified treatment by continuous subcutaneous insulin infusion is initiated.[1-5] The transient appearance of cotton-wool spots (soft exudates), considered to represent signs of ischaemia, was a prominent feature of these changes. The pathogenetic cause is not known, but a haemodynamic model of explanation has been suggested by various authors: a rapid change toward normo- or hypoglycaemia might reduce the blood flow to insufficient levels of perfusion.[1-3 5-7]

Adjustments of calibre of arteries and veins are part of the autoregulatory mechanisms responsible for a constant blood flow to the retina.[8 9] Increased blood flow[10 11] and vasodilatation[12] have been found in acute hyperglycaemia, and increased flow[13-16] and vasodilatation[16-20] have been registered in diabetic patients. Whether the circulatory changes are related to hyperglycaemia per se and/or to other factors of the disease is not clear. It seems most important to clarify vascular retinal reactivity to variations in both acute and long-term changes in metabolic control.

In a prospective and randomised trial insulin dependent diabetic patients in the Oslo Study,[4 5] were assigned to either continuous subcutaneous insulin infusion, multiple injections, or to conventional insulin treatment. By means of a computerised microdensitometric technique on fundus photographs[21 22] we studied the calibre of retinal vessels during one year of strict glucose control. This technique also measured the central 'light reflex', which represents the light reflected from the streaming column of erythrocytes. This reflex is of circulatory interest It has been shown that the intensity of reflection in arteries and veins and the width of the reflex in veins are significantly lower in diabetic patients than in normal controls.[23] The effect of near normoglycaemia on this reflex was examined. Further, we identified some vascular characteristics in patients at risk of developing cotton-wool spots during exposure to rapidly improved metabolic control.

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Table 1 *Clinical characteristics after randomisation to three treatment groups (mean and range)*

Treatment groups	*Sex (M/F)*	*Age (years)*	*Duration (months)*	*HbA₁ (%)*	*Systolic BP (mmHg)*	*Diast BP (mmHg)*	*IOP* (mmHg)*
CIT (n=15)	7/8	26 (18–36)	152 (81–240)	9·5 (7·6–14·6)	125 (110–150)	78 (70–95)	13·1 (9–19)
MI (n=15)	7/8	26 (19–42)	154 (81–250)	9·4 (7·0–11·7)	124 (110–140)	80 (60–95)	13·2 (9–18)
CSII (n=15)	7/8	26 (18–38)	153 (77–280)	10·1 (8·0–12·9)	123 (110–160)	81 (70–100)	13·0 (9–18)

*Mean value of both eyes

Subjects and methods

SUBJECTS

Forty-five insulin dependent diabetic patients (the Oslo Study[4,5]) were included. The clinical characteristics, the inclusion criteria, and the randomisation procedure have previously been presented in detail[5] In summary, the patients were randomly, at time 0, divided into three treatment groups: CIT: conventional insulin treatment (2 daily insulin injections); MI: multiple insulin injections (4–6 times daily); and CSII: continuous subcutaneous insulin infusion. To balance the groups, computerised matching was performed. It was based on the following criteria sex, age, diabetes duration, metabolic control (Table 1), and retinopathy (grade 1, no retinopathy; grade 2, one to three microaneurysms or haemorrhages; grade 3, more than three microaneurysms or haemorrhages; and grade 4, grade 3 plus hard exudates). Patients with proliferative retinopathy were not included. The one eye (denoted the primary eye) with the best visual acuity or the smallest refractive error, or both, was selected for vessel measurements. One eye was selected at random if no differences were found. Visual acuities were 20/20 in all primary eyes, and the range of refractory errors was from +0·5 to −4·0 dioptres with a mean of −0·8 dioptres.

OPHTHALMIC EXAMINATIONS

All examinations relevant to this study were performed two months before randomisation (preperiod), at the time of randomisation (time 0), and 3, 6, and 12 months later. The examinations included fundus photography of both eyes and fluorescein angiography of the primary eye. Furthermore, both eyes were scrutinised for cotton-wool spots by indirect ophthalmoscopy and binocular microscopy.

BLOOD PRESSURE AND INTRAOCULAR PRESSURE

Diastolic and systolic blood pressure and intraocular pressure were registered shortly before and shortly after fundus photography, respectively. The intraocular pressure was measured in cycloplegia. This was done to obtain pressures as representative as possible of the state of the eye at the moment of fundus photography (for comparable vessel measurements). Comparable results of mean values and ranges were obtained in the three treatment groups (Table 1).

METABOLIC CONTROL

Haemoglobin A_1 was estimated by an agar gel electrophoresis method[24] Mean blood glucose values were calculated by weekly capillary blood sampling on filter paper[25] before and 90 minutes after each meal, at bedtime, and in the morning. In a two-month preperiod home monitoring of blood glucose was introduced. Metabolic control was estimated at the same time intervals as described for the ophthalmic examinations. Blood glucose was also determined at exactly the same time as photography of the fundus.

METHODS

Densitometry across vessels in fundus photographs has been found to be an objective and sensitive method of measuring calibre.[26,27] Our photographic[22] and computerised microdensitometric[21] techniques have recently been described elsewhere. A short summary is presented here.

A 30° 'standard' fundus photograph of the primary eye was produced by centring the photograph at one-half the distance between the fovea and the temporal edge of the optic disc. An interference filter with a maximum transmission peak at 535 µm was inserted in the light path of the Zeiss camera, and a 35 mm Kodak Plus-X panchromatic type 5062 film was used. A 48-step density wedge was photographed and developed together with each film. A true calibration for transformation from film density into a linear intensity scale was obtained. The measured widths presented in this paper are expressed as micrometers (µm) on the retina.

In each photograph three arteries and three veins were analysed. We selected vessels having a straight course in the retina and chose the largest and two middle-sized vessels. Using a Nikon profile projector and anatomical landmarks in the pictures, we selected specific sites on the vessels and marked them directly on the negatives. Since we studied both the calibre and the light reflex, we did not use the

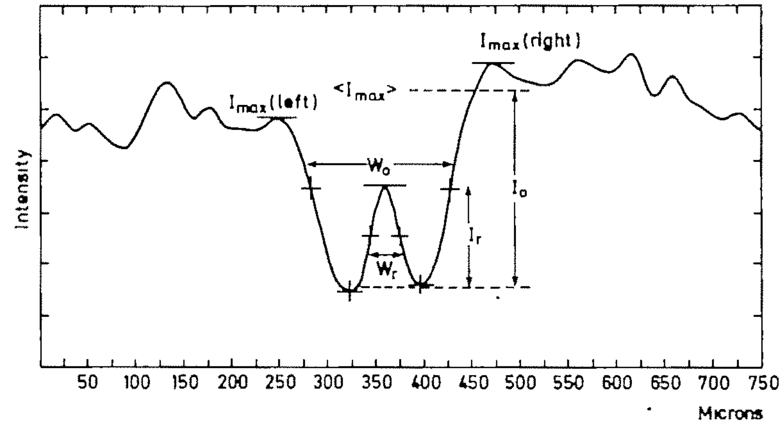

Fig. 1 A typical scan profile across a retinal vessel showing the background retina, the vessel absorption, I_0, and the central light reflex. I_0 is measured from an average background intensity level, (I_{max}), and the width of the blood column, W_0, is measured at half minimum intensity of I_0. The width of the light reflex, W_r, is measured at half maximum intensity of the peak intensity of the reflex, I_r. (From Brinchmann-Hansen and Engvold.[21])

fluorescein angiograms for measurements. The fluorescein technique does not produce central light reflexes.

We used a computer controlled microphotometer (a 288 K memory HP-21MX computer and a Heidenhain optical encoder) for scanning across the vessels and for data processing. The positional accuracy of the instrument was better than 1 μm. The scan contained 512 or 1024 data points, the scanning aperture was 5 μm wide (in the scanning direction), and the height mostly used was 250 μm. The microphotometry data were read from the magnetic tapes, converted from film transmission to relative intensity, and viewed with a display unit.

A typical scan profile is shown in Fig. 1. By means of a cross-hair cursor the background intensity levels were chosen on either side of the vessel and the other parameters were then derived by the computer. The depth of the vessel absorption relative to the average retinal background (I_0) was measured. The width of the vessel, W_0 (=the red blood cell column), was determined at the full width of the vessel absorption at half minimum intensity of I_0. The width of the light reflex (W_r) is measured at half maximum intensity of the peak intensity of the reflex, I_r. The ratio of the widths, W_r/W_0, is used in this study, and the I_r is expressed as relative values. The fundus photography was not synchronised to pulse characteristics, but the randomly exposed pictures should not give any systematic errors.

STATISTICS

A two-sided Wilcoxon rank sum test was used to compare mean values in different treatment groups, and a two-sided Wilcoxon signed rank test to compare means within the same group. A two-sided Fisher-Irwin exact test was used to compare frequencies. The level of significance was set at 5%. In calculating correlations between calibre of vessels and various clinical characteristics in the 45 patients, the non-parametric Kendall's τ method was used.[22]

Results

RETINOPATHY

The changes in retinopathy have previously been published.[5] A masked quantitative evaluation of colour fundus photographs (both eyes) showed a transient increase in number of microaneurysms and haemorrhages after three months' treatment by CSII. Masked ranking of fluorescein angiograms (primary eyes) showed a progressive deterioration on CIT, no changes on MI, and a transient worsening at three months on CSII.

During six months' treatment eight patients on MI and seven on CSII had developed cotton-wool spots in either one or both eyes. No cotton-wool spots were seen in patients on CIT, and no new spots developed at 12 months in any of the treatment groups. Patients developing cotton-wool spots (n=15) were characterised by a longer duration of diabetes and by more retinopathy at the start of the study than patients without cotton-wool spots on MI and CSII.[5] No age differences were noted (mean±SEM) in subjects developing cotton-wool spots, 26·3±1·3 years compared with subjects without cotton-wool spots, 26·0±2·0 years.

BLOOD PRESSURE AND INTRAOCULAR PRESSURE

No significant differences or changes in these parameters were found between treatment groups, between subjects with and without cotton-wool spots, or within each group throughout the study.

METABOLIC CONTROL

In the two months before treatment a lowering of haemoglobin A_1 was found in all treatment groups ($p<0·01$) (Fig. 2). After three months' treatment

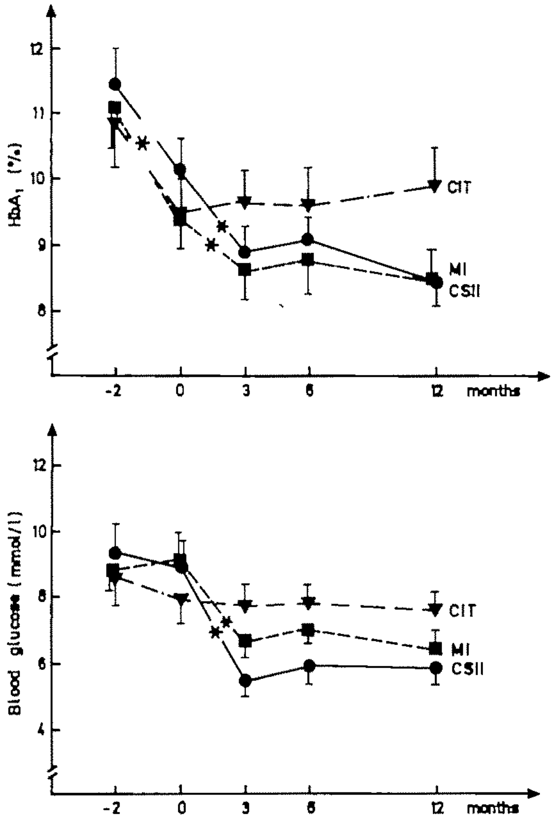

Fig. 2 *Metabolic control through the course of the study. Mean values; vertical bars. SEM. Decrease from preceding value within the treatment groups. * denotes p<0·01. The improved metabolic control between 3 and 12 months is statistically significant. HbA$_1$: CIT vs MI (p<0·05) and CIT vs CSII (p<0·01). Blood glucose· CIT vs MI (p<0·01) and CIT vs CSII (p<0·01).*

significant reductions in haemoglobin A$_1$ and mean blood glucose values were found in the MI and the CSII groups (p<0·01), but not in the CIT group. The difference in improved control between intensified regimens and conventional treatment was sustained from 3 to 12 months treatment.

At three months patients developing cotton-wool spots had a greater decrease in haemoglobin A$_1$ (−3·3±0·5 and −1·3±0·5) and mean blood glucose (−3·6±0·5 and −1·6±0·6) than those on MI and CSII treatment who did not (p<0·01).

Table 2 *Correlations between mean calibre of retinal vessels and various clinical characteristics in the 45 diabetics at the start of the study (Kendall's τ*)*

Clinical parameters	*Mean calibre*	
	Arteries	*Veins*
Sex	—	—
Age	—	0·32
Duration of disease	—	—
HbA$_1$	—	—
Blood glucose value†	—	—
Systolic blood pressure	—	−0·21
Diastolic blood pressure	—	−0·26
Intraocular pressure	—	—
Retinopathy grading	—	—

*The coefficient (τ) is presented when present on a statistical significant level of p≤0·05—corresponding to a τ value of ≥0·20
†Determined at the instant of calibre measurements
—, not significant.

CALIBRE OF VESSELS (W$_0$)

In the 45 subjects at the start of the preperiod a positive correlation between calibre of veins and the age of the patients (τ=0·32; p<0·05) and a negative correlation between calibre of veins and the diastolic (τ=−0·26; p<0·05) and the systolic (τ=−0·21; p<0·05) blood pressure were found (Table 2).

The distribution of calibre measurements in the three treatment groups at the start of the study is shown in Table 3. Comparable mean values and ranges of W$_0$ between groups were found. No changes in retinal arteries and veins were found in the treatment groups during the course of the study (Table 3).

In patients on MI and CSII those with cotton-wool spots were characterised by having greater initial calibre of retinal arteries (p<0·01) and veins (p<0·001) than patients without cotton-wool spots (Fig. 3). Among subjects having an average vein diameter ≥140 μm eight of 10 (80%) developed cotton-wool spots, compared with seven out of 18 (39%) in subjects with diameter of <140 μm. Although a significant long-term improvement in metabolic control was obtained, especially in patients with cotton-wool spots, no changes in either arteries

Table 3 *The calibre of retinal vessels during the course of the study (mean±SEM)*

	Months				
	−2	*0*	*3*	*6*	*12*
Arteries W$_0$ (μm)*					
CIT (n=15)	114±4	109±4	114±4	115±5	112±5
MI (n=15)	116±4	115±3	116±4	113±7	117±6
CSII (n=15)	116±4	118±4	116±4	116±4	113±4
Veins W$_0$ (μm)*:					
CIT (n=15)	129±6	125±4	135±7	132±5	129±6
MI (n=15)	133±8	127±8	131±9	134±9	133±8
CSII (n=15)	131±4	132±6	132±5	131±6	129±6

*Mean values of three arteries and three veins in each patient or veins were observed during 12 months of treatment (Fig. 3).

LIGHT REFLEX (W_r/W_0 AND I_r)

No differences and no changes in the width of the reflex (W_r/W_0) were found between the groups, in patients with and without cotton-wool spots or throughout the course of the study (Table 4). From randomisation to the end of six months' treatment a decrease in I_r in the intensified regimens (MI and CSII) occurred in both arteries and veins ($p<0{\cdot}01$).

At the start of the study I_r in both arteries ($p<0{\cdot}01$) and veins ($p<0{\cdot}01$) was more intense in subjects on MI/CSII developing cotton-wool spots than in those who did not (Fig. 4). Furthermore, subjects with cotton-wool spots were characterised by a greater increase in intensity during the preperiod in arteries ($p<0{\cdot}05$) and during the preperiod and after three months of intensified treatment in veins ($p<0{\cdot}05$). A significant decrease in I_r was seen from three to six months in both arteries ($p<0{\cdot}05$) and veins ($p<0{\cdot}01$) in patients with cotton-wool spots.

Discussion

Increased retinal blood flow and vasodilatation may be important in the progression of diabetic retinopathy.[32-34] A reversal of venous dilatation has been reported with improvement of metabolic control.[35] We found, however, that the calibre of arteries and veins was unaffected by intensified insulin treatment, by significant lowering of blood glucose levels, and by slow progression (CIT) and transient (CSII) worsening in retinopathy. In agreement with our findings, Hickam and Frayser found no diameter changes in retinal vessels during glucose infusion in normal

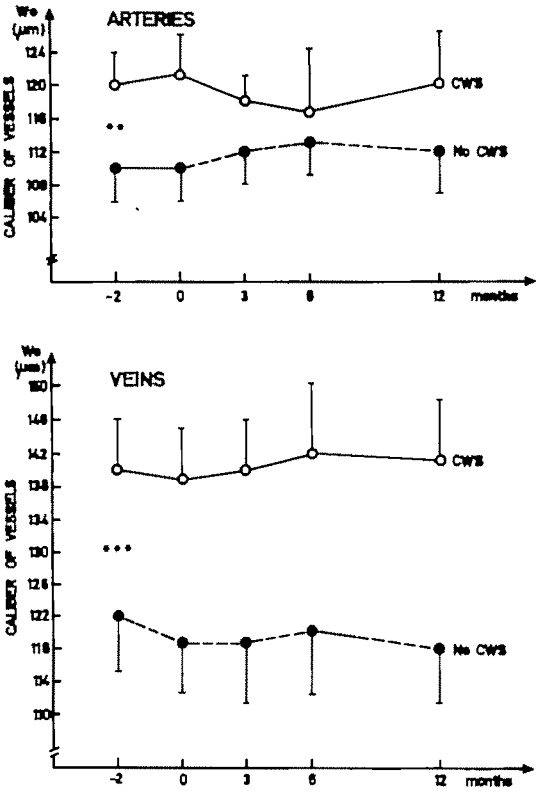

Fig. 3 *Calibre of retinal vessels (mean of three arteries and three veins in each subject) through the course of the study. Pooled data on subjects on MI and CSII are used. Mean±SEM in subjects with cotton-wool spots (CWS), n=15, and in subjects without (No CWS), n=15, are presented. Differences in initial size of vessels ** denotes p<0·01 and *** denotes p<0·001*

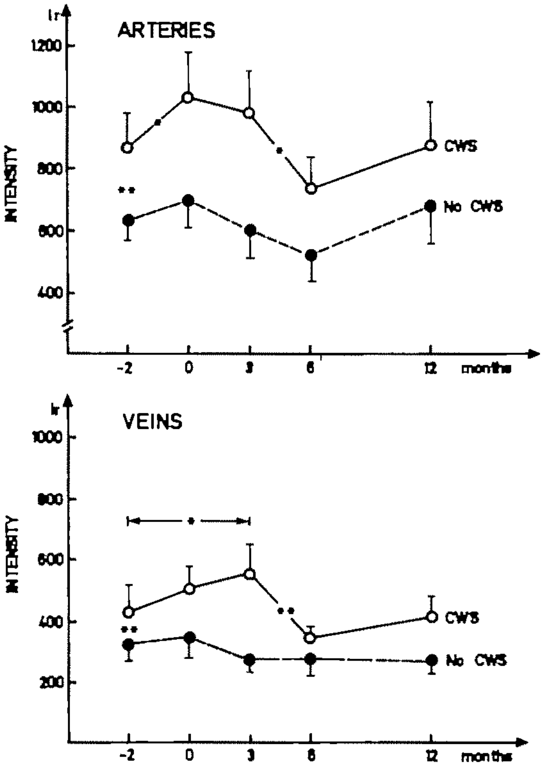

Fig. 4 *The intensity of the light reflex (I_r) through the course of the study. Measurements derived from the same scans as used in Fig. 3. Mean±SEM in subjects on MI/CSII with cotton-wool spots (CWS), n=15, and in subjects without (No CWS), n=15, are presented. Significant differences between CWS and No CWS subjects at start and in CWS subjects from −2 to 6 months are denoted: * p<0·05; ** p<0·01.*

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Usually one drop 0.25% solution in affected eye twice a day. If necessary, change to one drop 0.5% solution twice a day.

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PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade.

Cardiac failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blockers should be withdrawn gradually.

Do not use in patients with soft contact lenses. Mydriasis resulting from use of 'Timoptol' with adrenaline reported occasionally. Potentially, hypotension and/or marked bradycardia may result from addition of 'Timoptol' to a calcium antagonist, rauwolfia alkaloid or beta-blocker.

Children: Not recommended. Data not available for use in children.

Nursing: Mother should either stop nursing or stop 'Timoptol'.

Pregnancy: Not studied; weigh benefit against possible hazards.

SIDE EFFECTS

Ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, and decreased corneal sensitivity. Visual disturbances, including refractory changes (due sometimes to withdrawal of miotics), diplopia, and ptosis.

Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, congestive heart failure, palpitation, cardiac arrest.

Bronchospasm (predominantly with pre-existing bronchospastic disease), respiratory failure, dyspnoea. Headache, asthenia, nausea, dizziness, depression. Hypersensitivity, rash, and urticaria.

Reactions with an unestablished relationship are ACMO, dry mouth, anorexia, dyspepsia, nausea, dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension, and retroperitoneal fibrosis.

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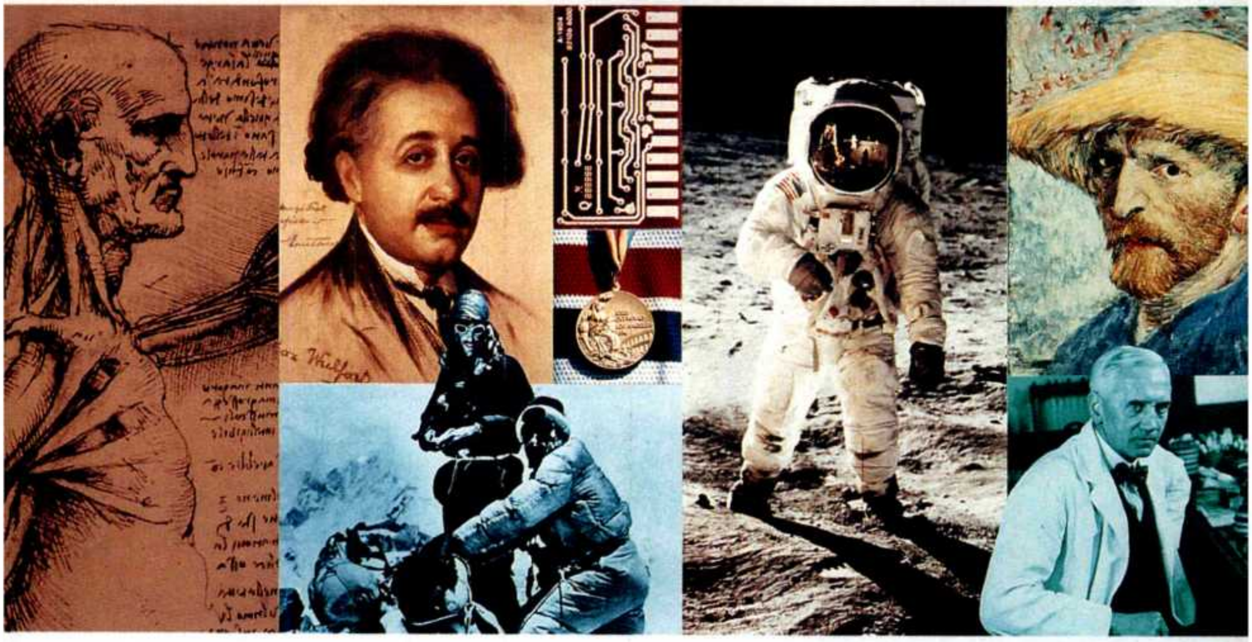

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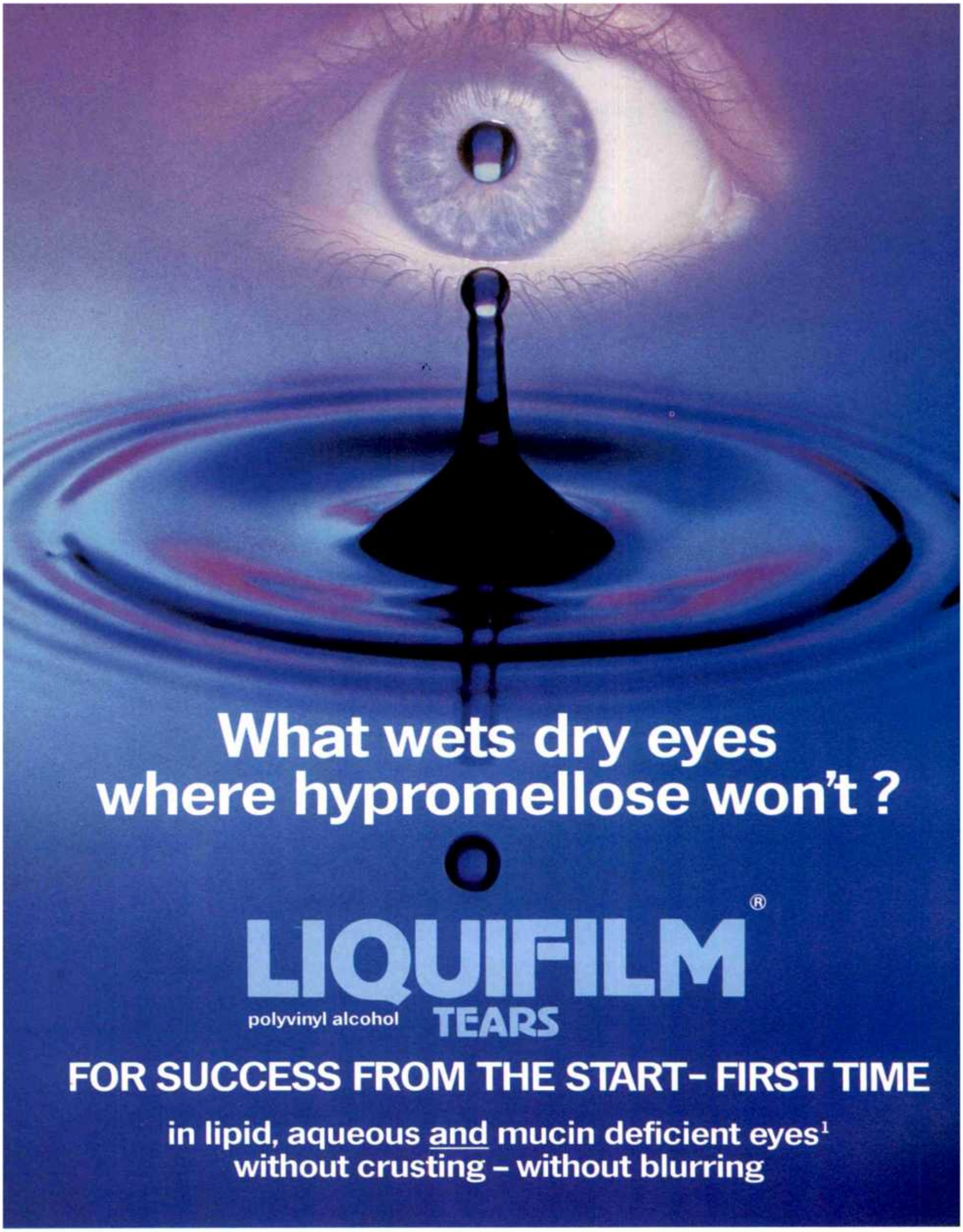

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Table 4 *The width (W_r/W_0) and the intensity (I_r) of the light reflexes during the course of the study (mean±SEM)*

	Months				
	−2	*0*	*3*	*6*	*12*
Width (W_r/W_0)*					
Arteries					
CIT	0·24±0·02	0·23±0·02	0·21±0·01	0·23±0·02	0·20±0·01
MI	0·22±0·01	0·20±0·01	0·23±0·02	0·20±0·01	0·20±0·01
CSII	0·19±0·01	0·21±0·01	0·21±0·01	0·19±0·01	0·19±0·01
Veins					
CIT	0·19±0·01	0·19±0·01	0·17±0·02	0·21±0·01	0·19±0·01
MI	0·20±0·02	0·18±0·02	0·17±0·01	0·19±0·02	0·18±0·02
CSII	0·17±0·01	0·19±0·01	0·19±0·02	0·19±0·02	0·20±0·02
Intensity (I_r)*					
Arteries					
CIT	704±86	865±91	744±65	777±41	667±67
MI	883±109	1009±122	894±109	732±101†	876±114
CSII	734±78	825±116	749±124	564±88†	709±109
Veins					
CIT	404±61	509±72	412±37	414±52	394±41
MI	423±77	422±70	416±83	304±51†	331±58
CSII	362±45	488±61	442±69	322±42†	371±57

*Mean values of three arteries and three veins in each patient
†Decrease from the start of randomisation (time 0) $p<0·01$

persons,[36] and Kohner *et al.* found no correlations between blood sugar levels and retinal volume flow in diabetic patients.[13]

This study thus indicates that middle-sized and large vessels are unresponsive to long-term changes in blood glucose levels per se, at least at this particular level of retinopathy. This interpretation, however, is complicated by the fact that retinal vessels in diabetic retinopathy have a reduced reactivity to substances known to be vasoactive.[27 37 38] Furthermore, although correlations have been found between flow and calibre changes,[39–41] some autoregulatory response may still have taken place. The small arterioles, which were not measured here, could have changed in diameter and affected the blood velocity.

Patients with the greatest diameters of retinal vessels seemed at risk of developing cotton-wool spots during intensified insulin treatment. We may speculate if diabetics with anatomically large arteries and veins are less capable of adapting to sudden metabolic and/or haemodynamic changes in the retina. Alternatively, patients developing cotton-wool spots suffered the greatest degree of prestudy 'chronic' vasodilatation; the stretching of the walls would impair the ability of the vessels to adapt their size according to needs.

LIGHT REFLEX OF THE VESSELS

A previous study has shown that our 45 diabetics, compared with a non-diabetic group, had narrower widths of the reflex (W_r/W_0) in the veins[23] In the present study return to nearly normal of the blood glucose did not 'normalise' the width. Favouring the intravascular blood column as the main reflecting surface producing the reflex, a recent theoretical study has shown that velocity/flow changes may influence the ratio W_r/W_0[42] Although this parameter is a rather coarse measure, it indicates that no significant haemodynamic changes occurred during the course of the study.

Physically, light reflection will occur only across surfaces of different refractive indices. Small changes in existing differences in indices between the streaming erythrocytes and the plasma of the retinal circulation may influence the intensity of the vascular reflex (I_r).[43] In comparison with normal controls, I_r was found to be significantly reduced in both arteries and veins in the 45 participants at the start of the study.[23] This could be explained by disturbances in the water shift from plasma to the erythrocytes[44 45] and in the composition of plasma proteins and plasma viscosity[45–47] which are found in diabetes. Increased mean corpuscular volume (MCV), elevated levels of plasma proteins, and probably a reduced intravascular pressure would all lower the I_r.[23]

Although the diameters of the streaming blood columns did not change, the intensity of the reflected light from these columns varied throughout the study. This indicates different intravascular effects of a rapid initial improved metabolic control (2–3 months) compared with a long-term (6–12 months) improved control. The association between changes in the intensity of the light reflex and changes in retinopathy indicates a role for haemorrheological factors in the progression of microangiopathy in diabetes. Local conditions in the eye (large vessels) might be of significance to the retinal response during tightening of the glucose control.

This study was supported by grants from the Norwegian Council on Cardiovascular Diseases, the Norwegian Heart and Lung Disease Association, the Norwegian Diabetes Association, the University of Oslo, the Norwegian Council for Science and the Humanities, and the Anders Jahres Medical foundation.

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Graves' ophthalmopathy: I. Simple CT estimates of extraocular muscle volume

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SUMMARY Graves' ophthalmopathy is an autoimmune inflammatory process affecting primarily the extraocular muscles. The enlargement of these muscles is responsible for most of the important manifestations of the disease, including proptosis, lid retraction, diplopia, and optic neuropathy. Recently the optic neuropathy has been shown to correlate with extraocular muscle volume as determined by computed tomography (CT). In the present study simplified measures of the extraocular muscles imaged by CT are described, which also correlate highly with the development of optic neuropathy.

Recently Feldon and coworkers[1] described a method for calculating the extraocular muscle volume of patients with Graves' ophthalmopathy, using high resolution computed tomographic sections. They demonstrated that the risk of developing optic nerve compression increased with extraocular muscle size and diminution of function.[2,3] Unfortunately the time and equipment necessary to calculate extraocular muscle volume limited the general application of this technique. The purpose of this paper is to explore alternative methods of determining extraocular muscle volume that might be more easily accomplished in the clinical setting.

Materials and methods

Computed tomographic scans were obtained from 152 orbits of 76 patients with Graves' ophthalmopathy. Some of these patients were included in prior studies.[1-3] Their average age was 50·1 years (range, 12 to 82); there were 14 men and 62 women.

APPARATUS

A GE 9800 or GE 8800 CT scanner was available for performing the orbital scans. In all but nine patients non-overlapping adjacent slices through the entire orbit (including roof and floor) were obtained in the axial plane at 1·5 mm intervals; in the nine patients slices were obtained at other intervals of 5 mm or less. The CT scans were imaged at window widths of 250 or 500 and at CT numbers of 0 to +20 Hounsfield units. These were quantitatively analysed with an image analyser.[1] An attached pen enabled contours to be traced and digitised for analysis. Packaged software provided with the image analyser was used to determine relative and absolute areas and volumes of structures by evaluating mid-orbital and serial two-dimensional sections.

PROCEDURE

Axial CT scans were obtained at an angle of 0 to −10° relative to the canthal-meatal line. Gentle eye closure was used to limit volume averaging produced by eye movement during the scan and to prevent asymmetric extraocular muscle contraction that might increase apparent muscle thickness. The filmed image of each slice was traced precisely. The bony orbit, extraocular muscle, optic nerve, and globe were outlined. In addition the 'muscle area' and the 'preseptal area' of the mid-orbital axial CT section, defined as that section imaging the crystalline lens, the optic nerve head, and the optic canal, were calculated separately. The muscle area was defined as the sum of the medial and lateral areas. The preseptal area was defined as all tissue anterior to a line connecting the lateral orbital rims, limited by the soft tissue laterally and the orbital wall medially. A cross-section of this mid-orbital cut was defined as

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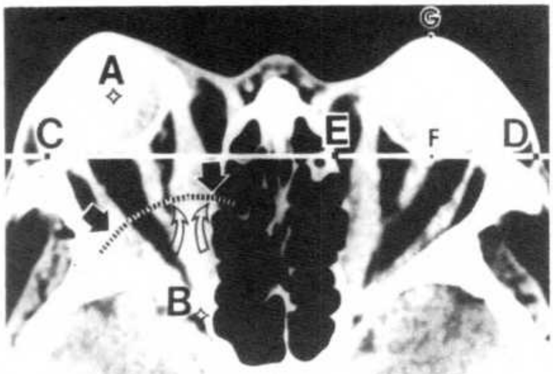

Fig. 1 *Mid-orbital section of a CT scan in a patient with Graves' ophthalmopathy. Point* A *is the centre of the globe. Point* B *is the orbital apex. The dashed arcline is equidistant from point* B, *including the midpoint of* AB. *Along the arc, orbital width (black arrows), medial muscle width (open arrows), and intraconal fat width are measured. Line* CD *is defined by the anterior extent of the lateral bony orbital rim. Preseptal area is calculated to include all tissue anterior to line* ED. *Proptosis is defined as the distance* FG.

Table 1 *Correlation of mid-orbital CT muscle areas with muscle volumes*

Muscle area	*Total EOM volume*	*Horizontal EOM volume*	*Vertical EOM volume*
Muscle area	0·89*	0·87	0·84
Medial rectus	0·88	0·87	0·81

*p<0·001 for r>0·36.
EOM=extraocular muscle.

an arc including the midpoint between the orbital apex and the geometric centre of the globe (Fig. 1). Along this cross-section, muscle width and the ratio of bony orbital width to intraconal fat width were calculated. Proptosis was defined as the distance between the apex of the cornea and a line connecting the lateral orbital rims as they appear on the mid-orbital axial section of the CT scan.

Orbital volumes were calculated by sequentially evaluating adjacent sections with the computed image analyser. Morphometric techniques were used that had previously been found to be accurate to within 7% to 10% for measurement of CT images. Errors due to volume averaging were minimised by using thin slices. In prior studies variation between individuals for singe muscles, estimated as the average ratio of single-muscle standard deviation to single-muscle mean volume, was 0·35.[1-3]

Because rectus muscles could not be reliably distinguished from adjacent extraocular muscles, the following pairs of muscles were analysed together: the levator and superior rectus, the superior oblique and medial rectus, and the inferior oblique and inferior rectus. The lateral rectus was analysed by itself. The volume of each muscle group was computed separately and compared with the overall volume of the orbit, after scaling the CT image so that the cross-sectional diameter of the globe on mid-orbital CT slice was made equal to 24 mm. In this study each muscle is referred to by the included rectus muscle.

Results

COMPARISON OF MUSCLE AREA OF THE MID-ORBITAL SECTION WITH EXTRAOCULAR MUSCLE VOLUME

A plot of total muscle area of the mid-orbital axial

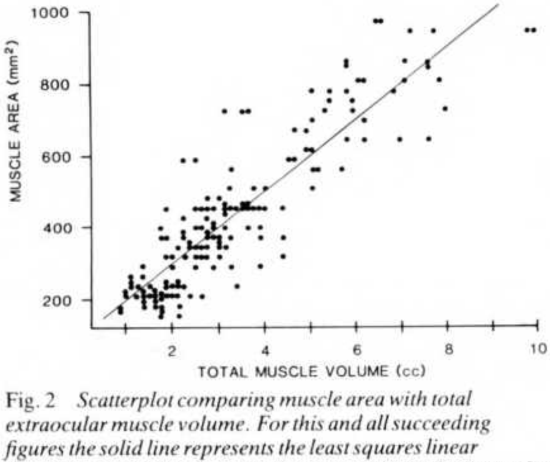

Fig. 2 *Scatterplot comparing muscle area with total extraocular muscle volume. For this and all succeeding figures the solid line represents the least squares linear regression and the horizontal axis represents total extraocular muscle volume.*

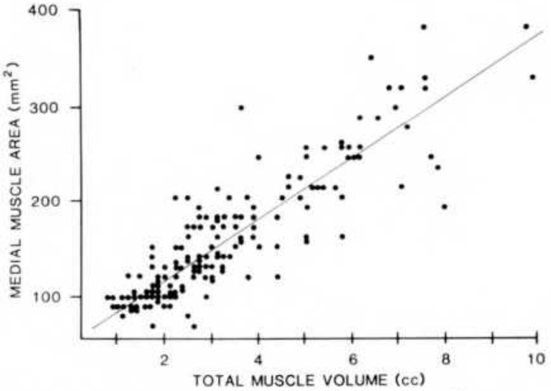

Fig. 3 *Scatterplot comparing medial rectus muscle area with total extraocular muscle volume.*

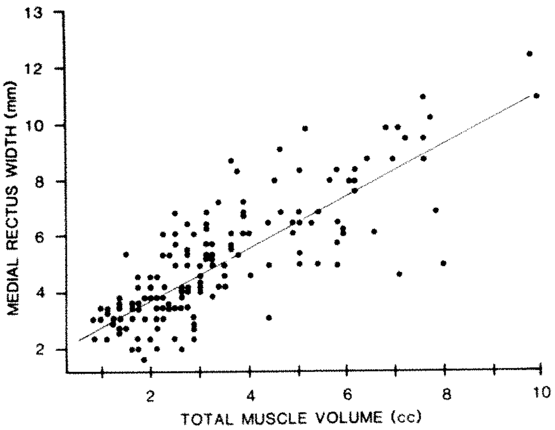

Fig. 4 *Scatterplot comparing medial rectus muscle width with total extraocular muscle volume.*

section ('muscle area') compared with total extraocular muscle volume is shown in Fig. 2. Least squares linear regression demonstrated a correlation between these two measures of 0·89. Correlations of muscle areas with total, horizontal, and vertical extraocular muscle volumes (all significant at p<0·001) are summarised in Table 1. A comparison of muscle area with horizontal muscle volume had a correlation of 0·87, and that of muscle area with vertical muscle volume had a correlation of 0·84. In comparing the area of just the medial rectus to the total muscle volume, shown in Fig. 3, the correlation was 0·88. Thus the area of the extraocular muscle, singly or together, imaged in the mid-orbital section appeared to reflect fairly accurately the total extraocular muscle volume.

COMPARISON OF MID-ORBITAL MUSCLE AND BONY WIDTH WITH EXTRAOCULAR MUSCLE VOLUME

Muscle width, a measure easier to obtain than orbital volume, was evaluated along an arc drawn through the mid-orbital point (Fig. 1). The plot of medial rectus muscle width compared with total extraocular muscle volume, shown in Fig. 4, gave a correlation of 0·80. Intraconal fat width was evaluated as a possible indirect measure of extraocular muscle encroachment on the optic nerve. However, the correlation with extraocular muscle volume was poor (r=0·16). The ratio of bony orbital width to intraconal orbital fat (orbit/fat ratio) along the arc subtended across the mid-orbital position was also calculated (Fig. 5), but had a better correlation (0·61) with total extraocular muscle volume (Table 2).

Table 2 *Correlation of other measures obtained on mid-orbital CT slice to muscle volumes*

Other measures	*Total EOM volume*	*Horizontal EOM volume*	*Vertical EOM volume*
Medial rectus width	0·80*	0·79	0·75
Preseptal area	0·79	0·75	0·78
Proptosis	0·65	0·61	0·63
Orbit/fat ratio	0·61	0·65	0·52
Intraconal width	0·16 (NS)	—	—

*p<0·001 for r>0·36.
EOM=extraocular muscle.

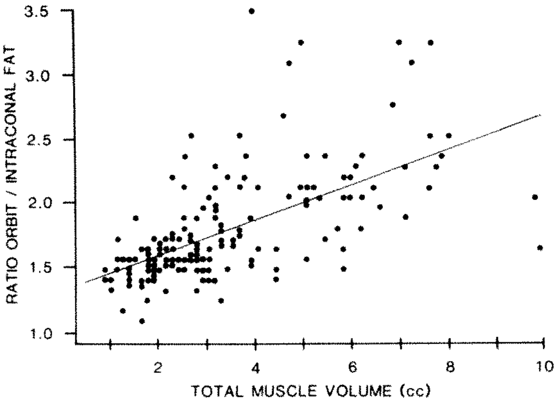

Fig. 5 *Scatterplot comparing the orbit/fat ratio with total extraocular muscle volume.*

INDIRECT MEASURES OF EXTRAOCULAR MUSCLE VOLUME

Periorbital swelling, known to correlate with extraocular muscle volume clinically,[2] was identified on the CT scan by determining the area of the preseptal tissue on the mid-orbital section. Correlation between the preseptal area on a mid-orbital CT slice and total extraocular muscle volume, as plotted in Fig. 6, was 0·79.

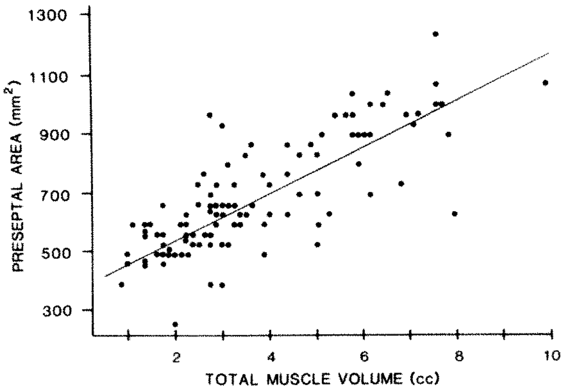

Fig. 6 *Scatterplot comparing the preseptal area with total extraocular muscle volume.*

Proptosis, measured from the CT scans directly rather than obtained clinically, was evaluated as a possible measure of extraocular muscle volume; correlation was 0·65. Correlations of the indirect measures with horizontal and vertical extraocular muscle volume, as well as with total extraocular muscle volume (significant at $p<0·001$), are summarised in Table 2.

Discussion

The principal alteration of the orbit in Graves' ophthalmopathy is enlargement of the extraocular muscles. This was first observed by Rundle and Pochin[4] in cadavers and later confirmed both intraoperatively by Naffziger[5] and radiologically by CT scan.[1-3 6-8] The importance of extraocular muscle volume in causing optic neuropathy in Graves' disease has been emphasised[6-8] and quantitatively assessed.[1-3 9]

Owing to the complexity and expense of obtaining and quantitatively analysing multiple thin axial CT sections, the development of alternative quantitative techniques for assessing the risk of optic neuropathy in Graves' ophthalmopathy is of clinical importance.[2 3] In our radiographic study we looked at several measures of the orbital tissues that might correlate well with total extraocular muscle volume, but which would be easier to obtain either by computing tissue areas from a single axial section or by simply using a curvilinear measure at a fixed anatomical location within the orbit. Our results suggest that high correlations exist between a variety of mid-orbital tissue areas or linear measures and total extraocular muscle volume. Although some of these measures could be determined manually by the ophthalmologist, most CT scanners have software that can be used to map areas and calculate distances on single sections. Ideally radiologists could provide this clinically important, quantitative information to the ophthalmologist. Even proptosis and periorbital swelling may be more reliably estimated from the CT scan, because CT measures seem to improve the correlation of these measures with extraocular muscle volume substantially ($r=0·65$ to $0·79$) compared with their clinically obtained counterparts ($r=0·29$ to $0·43$).[2 10]

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Graves' ophthalmopathy: II. Correlation of clinical signs with measures derived from computed tomography

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SUMMARY Quantitative clinical and computed tomographic (CT) measures of Graves' ophthalmopathy were obtained in 76 patients. Significant correlation of several CT parameters of the mid-orbital axial CT slice with optic nerve involvement was established. By means of clinical measures, only limitation of ocular motility was found to correlate with the optic neuropathy. The results suggested that there were two distinct populations of patients with Graves' disease which could be segregated by CT scan and clinical evaluation, one which developed optic neuropathy and one which did not. Therefore simple measures performed on the mid-orbital slice of the CT scan are recommended for all patients with Graves' ophthalmopathy as an important adjunct to careful evaluation of extraocular muscle function, in order to identify patients at risk of developing optic neuropathy.

Computed tomography is a useful technique in the assessment of Graves' ophthalmopathy.[1-4] When used in association with limitation of extraocular muscle function, computation of total extraocular muscle volume on CT identifies the population at risk for developing optic neuropathy.[5-7] However, several quantitative measures other than total extraocular muscle volume have now been shown to be highly correlated with total volume. These new measures are much easier and faster to obtain by either automatic or manual techniques of analysis.[8] The purpose of this paper is to correlate these other CT-derived measures with clinical manifestations of Graves' ophthalmopathy. In so doing, an optimal technique for assessing patients with Graves' ophthalmopathy can be established.

Material and methods

One hundred and fifty-two orbits in 76 patients with Graves' ophthalmopathy were studied and have been described in a companion paper.[8] An analysis of CT scans was performed, consisting of the quantitative estimation of extraocular muscle volume, mid-orbital extraocular muscle area (the area of medial and lateral recti being added together), mid-orbital medial rectus muscle area, and width (Fig. 1). Furthermore, on the mid-orbital axial CT slice (defined as that section imaging the crystalline lens, the optic nerve head, and the optic canal) preseptal area, proptosis, and the ratio of orbit to fat were calculated. The derivation of these CT measures has been described in detail elsewhere.[8]

In addition to CT analysis the following clinical signs of Graves' ophthalmopathy were evaluated: proptosis, periorbital oedema, lid retraction, lid lag, limitation of ocular motility, and optic neuropathy. Proptosis was measured with the Krahn exophthalmometer. Periorbital oedema was assessed in 112 of the orbits by measuring herniation of the upper lid tissue over the upper lid fold. Lid retraction was established as the exposure of sclera superior to the corneal limbus. Lid lag was measured in a manner similar to lid retraction, but with the eyes directed downwards (Fig. 2). Limitation of ocular motility was calculated as a percentage of full excursion in both horizontal and vertical directions of gaze. The semi-quantitative techniques used to determine the clinical

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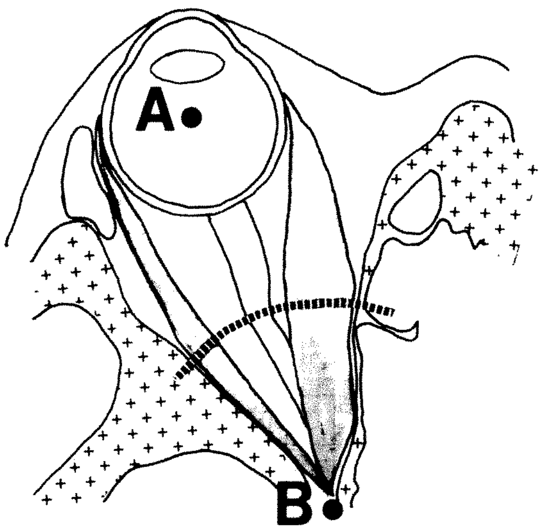

Fig. 1 *Camera lucida drawing of the mid-orbital axial slice of a CT scan. Point A is the centre of the globe. The dashed arcline is equidistant from the orbital apex* (B) *including the midpoint of* AB. *Along the arc medial muscle width and orbit-fat ratio were calculated.*

signs of Graves' ophthalmopathy have been described in detail elsewhere.[5 6]

Optic neuropathy was defined by the signs of optic nerve head swelling or atrophy, the presence of afferent pupillary defect, the loss of acuity or colour vision, or the presence of visual field defects not attributable to other eye disease. Patients were categorised as having *no optic neuropathy* (group 1, 50 patients), having *developed optic neuropathy* during follow-up (group 2, 13 patients), or having *presented with optic neuropathy* (group 3, 13 patients). The minimum follow-up time was six

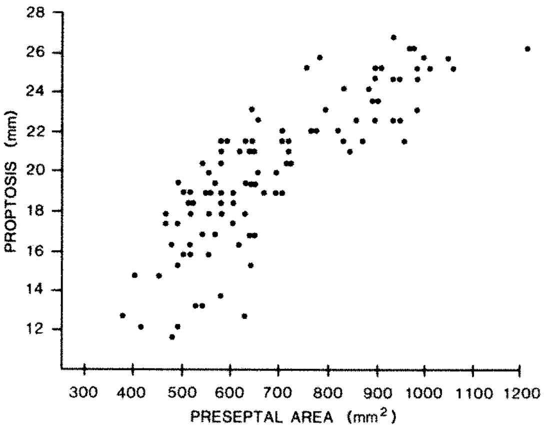

Fig. 3 *Scatterplot demonstrating the relation between proptosis and preseptal area both measured by quantitative CT analysis. Proptosis shows a linear increase with preseptal area only through about 70% of its full range.*

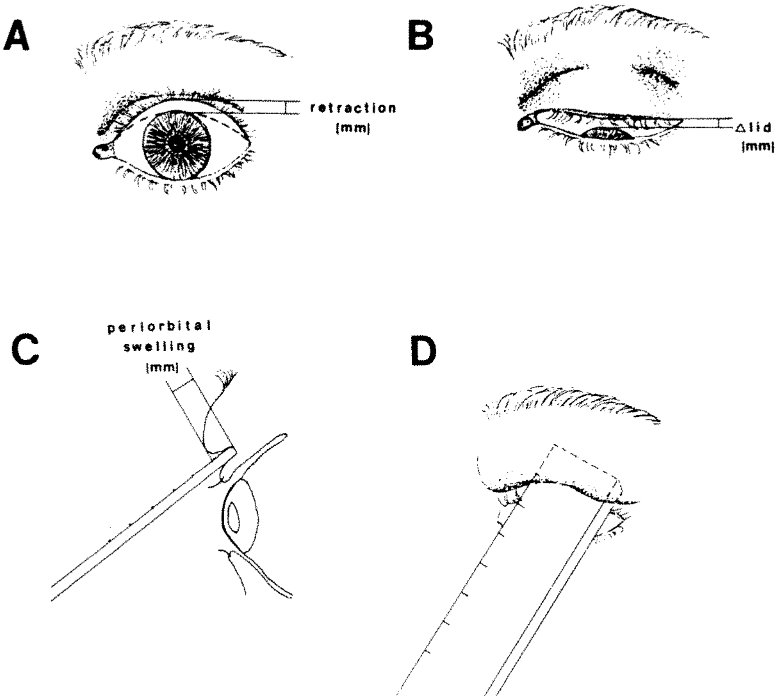

Fig. 2 *Semiquantitative techniques for evaluating clinical signs of Graves' ophthalmopathy are shown.* A: *The distance between the superior limbus and lid with eye in primary position of gaze is lid retraction.* B: *This distance measured in downgaze is lid lag.* C, D: *The distance between the lid fold and the anterior extension of the periorbital tissue of the upper lid is the measure of periorbital oedema.*

Table 1 *Correlation of clinical and CT signs of Graves' ophthalmopathy*

	Optic nerve involvement (p)	*Motility limitation (p)*	*Periorbital oedema (p)*	*Exophthalmometry (p)*	*Lid retraction (p)*	*Lid lag (p)*
CT measurements						
Muscle area	0·65 (p<0·001)*	0·40 (p<0·001)	0·46 (p<0·001)	0·39 (p<0·001)	0·10 (NS)	0·00 (NS)
Total muscle volume	0·65 (p<0·001)	0·46 (p<0·001)	0·43 (p<0·001)	0·43 (p<0·001)	0·15 (NS)	0·01 (NS)
Medial rectus width	0·61 (p<0·001)	0·55 (p<0·001)	0·44 (p<0·001)	0·29 (p<0·01)	0·11 (NS)	0·07 (NS)
Medial muscle area	0·57 (p<0·001)	0·51 (p<0·001)	0·49 (p<0·001)	0·45 (p<0·001)	0·17 (NS)	0·03 (NS)
Orbit/fat ratio	0·54 (p<0·001)	0·44 (p<0·001)	0·28 (NS)	0·18 (NS)	0·10 (NS)	0·01 (NS)
Preseptal area	0·42 (p<0·001)	0·36 (p<0·001)	0·47 (p<0·001)	0·57 (p<0·001)	0·16 (NS)	0·14 (NS)
Proptosis	0·28 (p<0·02)	0·26 (p<0·02)	0·37 (p<0·01)	0·73 (p<0·001)	0·16 (NS)	0·13 (NS)
Clinical signs						
Motility limitation	0·45 (p<0·001)	—	0·32 (p<0·02)	0·18 (NS)	0·21 (NS)	0·09 (NS)
Periorbital oedema	0·35 (p<0·01)	0·32 (p<0·02)	—	0·29 (NS)	0·06 (NS)	0·00 (NS)
Exophthalmometry	0·14 (NS)	0·18 (NS)	0·29 (NS)	—	0·10 (NS)	0·01 (NS)
Lid lag	0·06 (NS)	0·09 (NS)	0·00 (NS)	0·01 (NS)	0·30 (p<0·01)	—
Lid retraction	0·00 (NS)	0·21 (NS)	0·06 (NS)	0·10 (NS)	—	0·30 (p<0·01)

*p Values >0·001 were not considered as significant because multiple correlation was performed

months. The group number was used as a continuous variable in estimating the degree of optic nerve involvement for the purpose of calculating correlations with other measures of Graves' ophthalmopathy.

Results

CORRELATION OF CLINICAL SIGNS WITH CT MEASUREMENTS

Clinical signs of Graves' ophthalmopathy were correlated with several quantitative measures determined from the CT scans. These results are summarised in Table 1. As expected, total extraocular muscle volume was highly correlated with the presence of optic neuropathy ($r=0{\cdot}65$, $p<0{\cdot}001$) and was also significantly correlated with proptosis, total extraocular muscle limitation, and orbital swelling. Similar high correlations with optic neuropathy were also obtained using either the muscle area ($r=0{\cdot}65$, $p<0{\cdot}001$) or the medial rectus muscle area ($r=0{\cdot}57$, $p<0{\cdot}001$). Interestingly, medial rectus muscle width showed the highest correlation of any CT measure with total limitation of extraocular muscle function ($r=0{\cdot}55$, $p<0{\cdot}001$), and was nearly as highly correlated as the more complex volume and area measures of the extraocular muscles with optic neuropathy ($r=0{\cdot}61$, $p<0{\cdot}001$) and periorbital oedema ($r=0{\cdot}44$, $p<0{\cdot}001$).

CORRELATION OF CLINICAL SIGNS WITH EACH OTHER

Clinical signs of Graves' ophthalmopathy were correlated with each other. The results are summarised in Table 1. Significant correlations were obtained only for clinical measures compared with the occurrence of optic neuropathy. Even so, total limitation of extraocular motility ($r=0{\cdot}45$, $p<0{\cdot}001$) and periorbital oedema ($r=0{\cdot}35$, $p<0{\cdot}01$) were less correlated with optic neuropathy than were many of the CT measures.

EXOPHTHALMOMETRY AND PERIORBITAL OEDEMA

Exophthalmometry, a frequently used but highly variable method[9,10] for quantitation of Graves' ophthalmopathy, showed poor correlation with optic neuropathy ($r=0{\cdot}14$, $p>0{\cdot}1$) and other clinical signs. Proptosis determined from the CT scans correlated significantly with neither optic neuropathy nor total limitation of ocular motility, but did correlate highly with Krahn exophthalmometry ($r=0{\cdot}73$). The preseptal area was defined as all tissue anterior to a line connecting the lateral orbital rims, limited by the soft tissue laterally and orbital wall medially. The preseptal area encompassed elements of both periorbital oedema and proptosis, and it was significantly correlated with optic neuropathy and other clinical signs, such as total limitation of motility and periorbital oedema.

A scatterplot comparing preseptal area with proptosis showed a linear relationship through about 70% of the total range of proptosis. After proptosis was maximal, preseptal area continued to increase. Therefore, preseptal area was a more effective quantitative measure of orbital swelling in Graves' ophthalmopathy than were Krahn or Hertel readings (Fig.3).

MEASURES IDENTIFYING PATIENTS AT RISK FOR OPTIC NEUROPATHY

An attempt was made further to compare the ability of various CT and clinical measures to confirm the presence or predict the development of optic neuro-

Table 2 *Evaluation of clinical and CT signs of Graves' ophthalmopathy in separating patients with and without optic neuropathy*

	No risk optic vs present neuropathy		*No risk optic vs developed neuropathy*		*Present optic vs developed neuropathy*	
	t	*p*	*t*	*p*	*t*	*p*
CT measurements						
Muscle area	9·88	p<0·0001*	6·33	p<0·0001	2·64	p<0·006
Total muscle volume	9·68	p<0·0001	6·74	p<0·0001	2·50	p<0·008
Medial rectus width	8·93	p<0·0001	6·79	p<0·0001	1·39	NS (p<0·09)
Medial muscle area	7·87	p<0·0001	5·66	p<0·0001	1·58	NS (p<0·07)
Orbit/fat ratio	7·33	p<0·0001	5·84	p<0·0001	1·06	NS (p<0·2)
Preseptal area	4·37	p<0·0001	4·32	p<0·0001	0·34	NS (p<0·4)
Proptosis	3·23	p<0·0001	2·92	p<0·003	0·13	NS (p<0·5)
Clinical signs						
Motility limitation	4·49	p<0·0001	5·68	p<0·0001	0·88	NS (p<0·2)
Periorbital oedema	3·59	p<0·0001	3·33	p<0·0001	0·26	NS (p<0·4)
Exophthalmometry	1·52	NS (p<0·07)	1·21	NS (p<0·2)	0·25	NS (p<0·5)
Lid lag	0·72	NS (p<0·3)	0·39	NS (p<0·4)	0·17	NS (p<0·4)
Lid retraction	0·21	NS (p<0·5)	0·49	NS (p<0·4)	0·52	NS (p<0·4)

*p Values >0·001 were not considered as significant because multiple correlation was performed

pathy. These comparisons were performed using multiple *t* tests Therefore, only p values less than 0·001 were considered statistically significant. These data are summarised in Table 2. Virtually all CT measures, including muscle width, could significantly (p<0·0001) distinguish the groups that either had or developed optic neuropathy from the group that did not have optic neuropathy. The only clinical measures that distinguished these groups were total limitation of extraocular motility and periorbital oedema.

Neither CT measures nor clinical measures of Graves' ophthalmopathy successfully differentiated between the group that presented with optic neuropathy and the group that developed optic neuropathy. Some nearly significant differences were detectable between these groups by CT measures of extraocular muscle area (p<0·006) or volume (p<0·008).

Discussion

Clinical and CT measures of Graves' ophthalmopathy have been compared, especially with regard to their relationship to optic neuropathy. All CT measures of extraocular muscle enlargement correlated significantly; muscle area and total muscle volume were the most highly correlated. The only clinical measures that correlated significantly with optic neuropathy were limitation of ocular motility and perhaps periorbital oedema, confirming a prior study.[6]

Along with other CT-derived measures, medial rectus width, which may be obtained manually, was reliably able to distinguish between the group that would develop optic neuropathy and the group that would not. There seemed to be no reliable way of distinguishing the group that developed optic neuropathy from the group that presented with optic neuropathy. Therefore it is likely that these groups were in fact the same population.

This study has established quantitative CT evaluation of the extraocular muscles and preseptal area as the most important parameters in assessing and following up patients with Graves' ophthalmopathy. Muscle area can be determined by the radiologist using morphometric analysis available on most CT scanners. Similarly, preseptal area is easy to calculate and is a better measure of anterior manifestations of Graves' ophthalmopathy than are either Krahn exophthalmometry or clinical evaluation of periorbital oedema. If automatic analysis is not available, medial rectus muscle width is an exceptionally easy measure to obtain manually for evaluating risk of optic neuropathy, requiring only a single mid-orbital thin CT section and no special equipment, training, or calculation.

Although many clinical signs are of value in diagnosing orbital involvement with Graves' disease, limitation of motility and optic nerve changes only need be regularly evaluated once a baseline orbital CT scan has been performed and measured.

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Graves' ophthalmopathy: III. Effect of transantral orbital decompression on optic neuropathy

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SUMMARY Twenty-five patients (48 eyes) underwent transantral, surgical decompression of their orbits for treatment of Graves' ophthalmopathy with optic neuropathy. Visual acuity improved in 77%, remained unchanged in 17%, and worsened in 6%. Colour vision improved in 76%, remained unchanged in 20%, and worsened in 4%. Visual fields improved in 67%, remained unchanged in 12%, and worsened in 22%. In general the worse the vision preoperatively the greater the relative improvement postoperatively. Clinical and radiological findings failed to correlate with visual outcome of surgical intervention. The study shows surgery to be highly effective in restoring optic nerve function for patients with severe Graves' ophthalmopathy.

The optimal treatment of optic neuropathy associated with Graves' ophthalmopathy is controversial. Systemic corticosteroids,[1-4] high energy irradiation,[5-8] and surgical decompression[9-13] of the orbit have all been advocated. Although most authors have reported beneficial effects on visual acuity from surgical decompression, its effects on other aspects of visual function have not been emphasised. The purpose of this report is to quantitate the effect of transantral orbital decompression on the visual acuity, colour vision, and visual fields of 25 patients with Graves' dysthyroid optic neuropathy who failed to respond to high dose systemic corticosteroids.

Patients and methods

PATIENTS

Twenty-five patients who underwent surgical decompression of their orbits for treatment of optic neuropathy secondary to Graves' ophthalmopathy were evaluated in a retrospective manner. Of these, 21 patients underwent a single bilateral procedure, two underwent a single unilateral procedure, and two underwent a second bilateral procedure. Nineteen patients were women and six were men; the average age was 58·8 years, range 27 to 83 years. All the patients were examined preoperatively for visual acuity by Snellen types, colour vision (AO pseudoisochromatic plates), and visual fields (15 patients by Octopus automated perimeter). In addition all the patients had CT scans, all but four of which were evaluated quantitatively to determine the extent of extraocular muscle enlargement.[14] Visual function tests were repeated at least once after surgery. Table 1 summarises the presenting features of each patient. The data were analysed by standard statistical techniques of correlation and linear regression. Visual fields were analysed by Octopus Program Delta. The average follow-up time was 18·5 months, ranging from a low of one to a high of 49 months.

SURGERY

Transantral orbital decompression was performed according to the technique described by Walsh and Ogura[11] and lateral orbital decompression by the technique described by Kroll and Casten.[10] All patients received at least two weeks of high dose (80–100 mg/day) methylprednisolone (prednisone) prior to surgery; this was gradually tapered for one to three weeks after surgery. Transient or permanent infraorbital anaesthesia was present in the majority of patients. Diplopia, not present preoperatively, was apparent after surgery in 7 of 12 patients. No instances of orbital cellulitis, leak of cerebrospinal fluid, orbital haemorrhage, or catastrophic visual loss were encountered.

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Table 1 *Presenting features of 25 patients*

Patient	*Age*	*Sex*	*Eye*	*VA*	*CV*	*Field loss*	*APD*	*ON*	*Propt*	*TA*	*Exp*	*% Lim*	*Strab*	*% Muscle volume*
1	66	F	R	20/800	0/15	20·1	+	1	22	20	–	59	25XT	15·6
			L	20/40	4/15	16·9	–	0	20	24	–	45		16·8
2	82	F	R	20/300	0/15	NA	+	4	22	24	+	63	Ortho	21·0
			L	*	*	*	*	*	*	*	*	*	*	*
3	39	F	R	20/50	8/15	NA	+	2	27	27	+	NA	10RHT	20·5
			L	20/30	4/15	NA	–	0	26	24	–	NA		18·2
4	53	F	R	20/40	11/15	21·6	–	0	22	28	–	41	10X(T)	12·6
			L	20/60	11/15	20·6	–	0	22	31	–	43		13·8
5	31	F	R	20/25	14/15	NA	–	0	25	23	+	71	Ortho	23·4
			L	20/25	12/15	NA	–	0	26	26	+	40		24·7
6	62	M	R	20/400	0/15	22·3	+	2	21	20	+	25	Ortho	23·0
			L	20/40	9/15	16·5	–	2	21	20	+	60		19·5
7	59	M	R	20/15	15/15	NA	–	2	25	21	–	100	Ortho	12·1
			L	20/25	15/15	9·5	+	4	23	30	–	55		18·1
8	56	M	R	20/40	13/15	0·4	+	3	29	16	–	57	14RHT	16·0
			L	20/30	15/15	0·0	–	3	27	17	–	64	8XT	14·2
9	61	F	R	20/80	9/15	12·5	+	0	26	20	–	66		NA
			L	20/60	12/15	NA	–	0	26	12	–	66	35LHT	NA
10	42	F	R	20/40	11/15	4·9	–	0	26	30	–	86	Ortho	19·0
			L	20/30	11/15	7·3	+	0	27	32	–	69		19·0
11	63	F	R	20/20	10/15	9·7	–	4	22	19	–	93	Ortho	17·0
			L	20/70	10/15	18·9	+	0	22	19	–	93		18·6
12	63	F	R	20/30	8/15	NA	–	2	26	15	–	45	11E(T)	17·4
			L	20/30	7/15	NA	+	2	27	16	–	45		16·4
13	83	F	R	20/200	10/15	NA	–	0	19	20	+	22	Diplopia	NA
			L	20/70	8/15	NA	–	0	19	18	+	29		NA
14	59	M	R	20/80	11/15	NA	–	0	9	24	–	35	Diplopia	11·9
			L	20/40	11/15	NA	–	1	7	25	–	41		14·0
15	51	F	R	20/20	12/15	0·0	–	3	25	20	–	43	sm XT	NA
			L	20/30	10/15	0·0	–	3	23	18	–	53		NA
16	75	F	R	20/200	0/15	NA	+	4	21	20	+	50	35ET	NA
			L	20/60	0/15	NA	–	0	19	20	+	43		NA
17	78	F	R	20/200	NA	19·9	–	3	28	19	+	38	Ortho	21·6
			L	20/400	NA	14·6	–	4	27	22	+	40		21·5
18	29	F	R	20/200	11/15	16·8	+	3	22	26	+	31	Ortho	13·2
			L	20/20	15/15	5·2	–	2	22	26	+	31		11·5
19	49	F	R	20/25	11/15	2·5	–	2	23	14	–	19	Ortho	14·5
			L	30/15	12/15	4·4	–	2	23	15	–	19		12·4
20	72	F	R	20/60	10/15	2·1	–	3	24	17	NA	33	Ortho	19·0
			L	20/60	10/15	2·3	+	0	26	17	NA	35		20·6
21	27	M	R	20/30	14/15	1·5	–	0	31	25	+	60	RHT	17·8
			L	20/50	13/15	3·0	–	0	30	20	+	60	10ET	15·2
22	74	F	R	10/100	2/15	NA	–	2	18	60	+	43	Diplopia	26·0
			L	20/200	2/15	NA	+	4	14	14	+	43		26·9
23	67	F	R	20/100	8/15	5·3	+	0	23	14	+	30	RHT	13·8
			L	*	*	*	*	*	*	*	*	*	*	*
24	74	M	R	20/30	10/15	NA	–	2	24	18	–	70	4RHT	14·5
			L	20/20	10/15	NA	–	2	27	20	–	48		12·7
25	54	F	R	20/25	10/15	NA	–	2	26	15	+	15	4RHT	10·7
			L	20/25	13/15	NA	–	2	25	15	–	38		9·0

VA=visual acuity CV=colour vision Field loss=mean decibel whole field loss APD=afferent pupillary defect. ON=optic nerve status (0=no neuropathy, 1=hyperaemia, 2=swollen, 3=partial atrophy, 4=atrophy) Propt =proptosis TA=tension applanatation Exp =exposure %Lim=total percentage muscle limitation Strab =Strabismus present.

XT=exotropia Ortho=orthotropia RHT=right hypertropia LHT=left hypertropia E(T)=intermittent esotropia ET=esotropia NA=not available *=Surgery not performed on that eye

Results

DIFFERENCES IN VISUAL FUNCTION FOLLOWING SURGERY

Of the 48 eyes that had surgery 37 (77%) had improvement in visual acuity postoperatively, eight (17%) showed no improvement (five of which had a preoperative visual acuity of 20/20 or better), and three (6%) worsened. Of the 25 eyes tested for colour vision pre- and postoperatively the colour vision

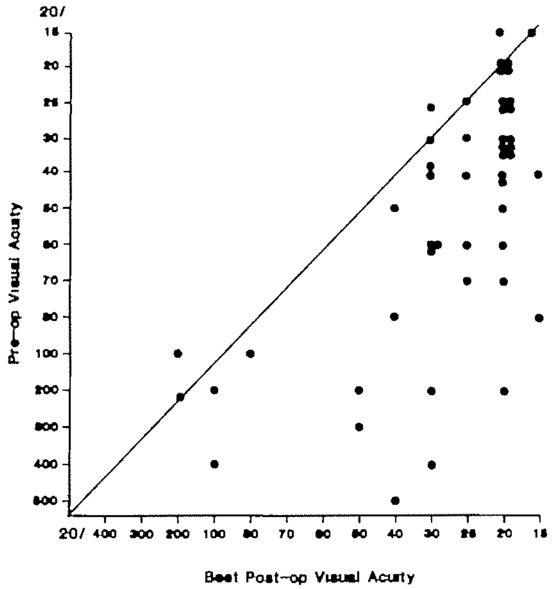

Fig. 1 *Scatterplot comparing pre- and postoperative Snellen visual acuity results ($t=-7{\cdot}02$, $p<0{\cdot}001$) For this and all succeeding scatterplots the solid line represents 'no change', points above the line denote a decrease, while points below denote an improvement.*

improved in 19 (76%), remained unchanged in five (20%) (two of which had a preoperative colour vision of 15/15), and deteriorated in one (4%). Of the eyes evaluated by Octopus automated perimetry there was quantitative improvement in 18 (67%), no change in three (12%) (all of which showed no preoperative loss), and an increased loss in six (22%).

A quantitative analysis of visual parameters was performed to determine the amount of change between the preoperative and postoperative assessment. Fig 1 compares the pre- and postoperative visual acuity by Snellen types for each patient. Fig. 2 compares the pre- and postoperative results of pseudoisochromatic testing of colour vision. In general, patients with higher degrees of visual loss preoperatively had greater improvement after surgery. This tendency was statistically significant, with correlations between preoperative visual acuity and postoperative change being $-0{\cdot}54$ ($p<0{\cdot}001$), between preoperative colour vision and postoperative change being $-0{\cdot}74$ ($p<0{\cdot}001$), between preoperative central 10° visual fields and postoperative change being $-0{\cdot}72$ ($p<0{\cdot}001$), and between preoperative whole visual fields and postoperative change being $-0{\cdot}60$ ($p<0{\cdot}001$).

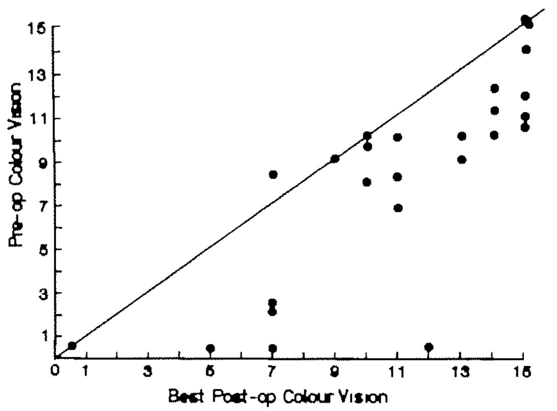

Fig. 2 *Scatterplot comparing pre- and postoperative pseudoisochromatic colour vision results ($t=-5{\cdot}33$, $p<0{\cdot}001$).*

ASSOCIATION OF NON-VISUAL AND VISUAL PARAMETERS WITH POSTOPERATIVE VISUAL IMPROVEMENT

Proptosis, limitation of extraocular motility, and extraocular muscle size on CT scan were evaluated as possible predictors of visual outcome following orbital decompression. However, correlations were nearly zero in each instance.

QUANTITATIVE ASSESSMENT OF VISUAL FIELDS

The type of visual field loss encountered preoperatively was studied by means of analysis by quadrants, whole 30° fields, and central 10° fields. The frequency of encountering visual loss of various degrees in these portions of the field are shown in Fig. 3. The frequency of improvement in visual fields postoperatively for each portion of the field is shown in Fig. 4. A significant correlation was found for postoperative improvement with preoperative severity for the whole field, the lower temporal, the lower nasal, and the central 10° of field. These correlations are summarised in Table 2.

Discussion

Quantitative analysis of several parameters of visual function in patients undergoing orbital decompression for Graves' ophthalmopathy with optic neuropathy suggests that surgery is highly effective in restoring all manifestations of optic nerve function—acuity, visual fields, and colour vision. This improvement is especially remarkable in this series of patients because the criterion for surgical decompression was either failure to improve on or drug intolerance to corticosteroids. Morbidity of the procedure was acceptable, with the major complications being diplopia and infraorbital numbness, as has also been reported by others.[11 13]

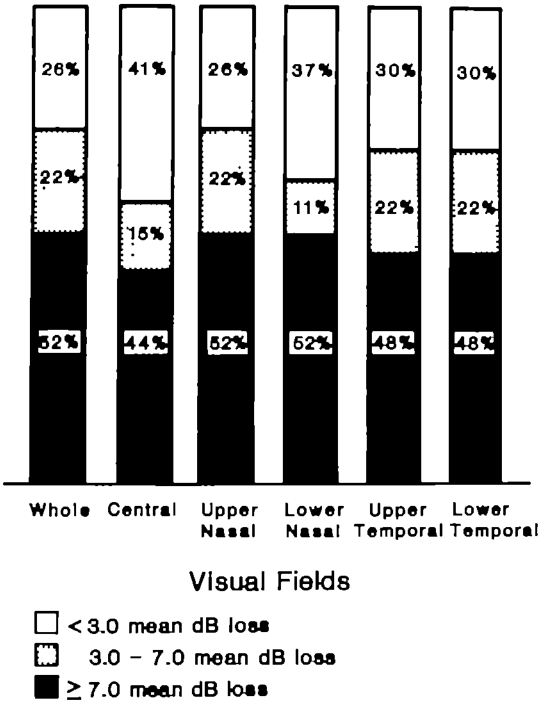

Fig 3 *Bar diagram demonstrating the frequency of preoperative visual field loss 27 eyes.*

Other than the finding first noted by Ogura *et al.*,[14] that patients with more severe visual dysfunction are more likely to show postoperative improvement, no other parameter of disease, such as preoperative proptosis, motility limitation, or even extraocular muscle enlargement by CT scan seems to aid in predicting which patients are likely to benefit substantially from surgery.

Similar studies to compare quantitatively the results of orbital decompression with other types of treatment for optic neuropathy in Graves' ophthalmopathy are needed. These additional studies should improve the treatment of this vision-threatening disease

Table 2 *Correlations between preoperative visual field mean decibel loss and postoperative improvement*

Visual field	*r*	*p*
Central	−0·72	<0·001
Lower temporal	−0·66	<0·001
Lower nasal	−0·63	<0·001
Whole	−0·60	<0·001
Upper temporal	−0·44	<0·05
Upper nasal	−0·37	NS

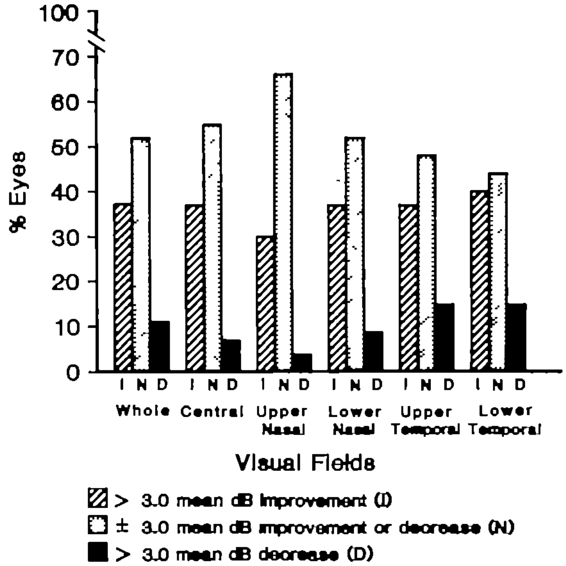

Fig. 4 *Bar diagram demonstrating the frequency of postoperative visual field improvement* I=*improvement,* N=*no change,* D=*decrease.*

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Pharmacokinetics of a 5-fluorouracil liposomal delivery system

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SUMMARY A liposomal delivery system was developed in an attempt to prolong ocular levels of 5-fluorouracil for glaucoma filtering surgery. The pharmacokinetics of the 5-fluorouracil liposomal delivery system were studied in normal pigmented rabbits with 5-fluorouracil labelled with carbon-14 (C-14). ^{14}C 5-fluorouracil was incorporated into the liposomes at a concentration of 10 g/l and injected subconjunctivally in doses of 5 and 10 mg. Concentrations of 5-fluorouracil were assayed at 10 time intervals from 0·5 to 96 hours in cornea, sclera, and conjunctiva and at six time intervals from 0·5 to 12 hours in aqueous. Two peak concentrations were noted at approximately one and eight hours, with measurable levels present at 96 hours. This study demonstrates the ability of this liposomal delivery system to prolong levels of 5-fluorouracial in normal pigmented rabbits.

5-Fluorouracil, a synthetic pyrimidine, has been shown to decrease fibroblast proliferation in vitro[1] and has been used clinically to treat proliferative vitreoretinopathy[2] and prevent the closure of conjunctival filtering blebs.[3,4] In preliminary studies 5-fluorouracil improved the final surgical outcome. Though various subconjunctival and intravitreal doses of 5-fluorouracil have been used, all have required frequent repetitive injections because of the short half-life of ocular 5-fluorouracil. These injections cause discomfort and inconvenience to the patient and carry the risk of haemorrhage, infection, conjunctival scarring, ocular perforation, and additional postoperative inflammation. The complications from these treatments include corneal and conjunctival epithelial toxicity.[2,3] This epithelial toxicity has caused treatment regimens to be altered or discontinued.[3] The peak concentrations of 5-fluorouracil obtained have been implicated as the cause of this toxicity.[5] Clinical success could be improved if the ocular half-life was increased and the peak concentration was decreased.

Microspheres in a variety of forms have been used successfully to prolong drug half-lives and diminish toxic side effects.[6] 5-Fluorouracil was incorporated into a liposomal matrix, and the ocular pharmacokinetics of a single subconjunctival injection investigated in normal pigmented rabbits.

Materials and methods

Carbon-14 labelled 5-fluorouracil (1050 nCi/mg) was incorporated into stabilised anionic liposomes at a concentration of 10 g/l. By liquid chromatography and distillate analysis 70% of the 5-fluorouracil was found to be incorporated with the liposomes and remained stable for longer than 168 hours. The liposomes consisted mainly of hydrogenated lipid phosphatides derived from egg. The phospholipids were composed of phosphatidylcholine (75%) and phosophatidylethanolamine (20%) with the primary fatty acids being stearate and palmitate. This system was found to be multilaminar by electron microscopy.

Dutch Belt pigmented rabbits (1·5–2·5 kg) were anaesthetised with a 0·7 ml intramuscular injection of ketamine (100 g/l) and acepromazine (1 g/l). The liposomal 5-fluorouracil was injected under the inferior bulbar conjunctiva with a 27 gauge needle. 5 mg (0·5 ml) and 10 mg (1·0 ml) of liposomal 5-fluorouracil were injected in the right and left eyes respectively. A conjunctival bleb was noted after each injection. The concentration of 5-fluorouracil

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Table 1 *Concentration of 5-fluorouracil following a 5 mg injection of liposomal 5-fluorouracil (μg/g)*

	Time in hours									
	0·5	*1*	*2*	*4*	*8*	*12*	*24*	*48*	*72*	*96*
Sclera	3393	2052	259	430	86·2	35·0	32·6	9·7	2·5	0·9
Conjunctiva 180° from inj.	112	109	24·1	8·7	16·7	5·5	0·9	2·1	0·7	0·3
Conjunctiva 0° from inj	15475	5453	1132	340	1401	191	143	63·0	62·6	32·0
Whole cornea	107	108	79·6	46·5	114	15·0	7·7	7·0	2·0	0·3
Central cornea	125	18·8	5·2	14·4	23·2	9·9	3·5	4·2	NA	NA
Aqueous	4·5	6·2	4·4	2·5	4·3	0·2	NA	NA	NA	NA

Table 2 *Concentration of 5-fluorouracil following a 10 mg injection of liposomal 5-fluorouracil (μg/g)*

	Time in hours									
	0·5	*1*	*2*	*4*	*8*	*12*	*24*	*48*	*72*	*96*
Sclera	5838	577	275	450	104	38·5	13·1	9·4	1·7	3·2
Conjunctiva 180° from inj	106	24·8	63·4	45·1	91·5	13·9	3·7	6·0	3·0	1·2
Conjunctiva 0° from inj	41457	34816	28406	4071	4070	272	195	57·0	90·0	37·0
Whole cornea	226	215	155	79·3	140	23·6	12·5	19·1	1·9	1·9
Central cornea	156	50·8	12·5	9·0	53·0	13·3	0·1	2·2	NA	NA
Aqueous	12·0	11·5	7·7	5·2	10·5	0·3	NA	NA	NA	NA

was measured at 10 time intervals (0·5, 1, 2, 4, 8, 12, 24, 48, 72, 96 hours) for conjunctiva, sclera, and cornea and at six time intervals (0·5, 1, 2, 4, 6, 12 hours) for aqueous. Two rabbits were used at each time interval except at 72 and 96 hours, when only one rabbit was employed.

At the specified time interval each rabbit was reanaesthetised with a 0·7 ml intramuscular injection of ketamine (100 g/l) and acepromazine (1 g/l). An aqueous sample of 0·15 ml was obtained from the anterior chamber through a 30 gauge needle. Two limbal conjunctival specimens were excised, one overlying and the other 180° from the liposomal 5-fluorouracil injection. Each rabbit was killed with a 3·0 ml intracardiac injection of euthanasia solution (Beuthanasia). After immediate enucleation the eyes were rinsed of overlying blood with normal saline and the specimens obtained. The sclera underlying the injection site was excised with a No. 15 Bard Parker blade. Central corneal or whole corneal specimens were removed with corneoscleral scissors.

All specimens and five samples of carbon-14 labelled liopsomal 5-fluorouracil were placed in scintillation vials and weighed with an analytical balance. All solid tissue specimens were dried prior to weighing. 50 μl of normal saline were added to each scintillation vial, allowance being made for rehydration of the tissue specimens. 1 ml of tissue solubiliser (Protosol) was added to each vial. When digested the solutions were neutralised with acetic acid, and 10·0 ml of scintillation fluid was added to each vial. The radioactivity of all the samples was recorded in a liquid scintillation counter. Ten control vials containing appropriate quantities of the reagents used were recorded to assess background radioactivity.

Results

The average concentration of 5-fluorouracil in the six ocular tissues studied after a 5 mg injection of liposomal 5-fluorouracil are displayed in Table 1. At 1, 8, and 96 hours following injection the average concentration of 5-fluorouracil and its metabolites was 109, 16·7, 0·3 μg/g in superior conjunctiva, 108, 114, and 0·3 μg/g in cornea and 3392, 86·2, 0·9 μg/g in sclera respectively. The peak aqueous concentration was 6·2 μg/g.

The average concentration of 5-fluorouracil in the samples studied following a 10 mg injection are shown in Table 2. At 1, 8, and 96 hours the average concentration of 5-fluourouracil and its metabolites was 106, 91·5, and 1·2 μg/g in superior conjunctiva; 215, 140, and 1·9 μg/g in cornea; and 577, 104, and 3·2 μg/g in sclera respectively. The peak aqueous concentration was 12·0 μg/g.

The average recorded background radioactivity was 14 cpm. This figure was subtracted from the scintillation recordings of each specimen. 0·1 μg of 5-fluorouracil was equivalent to 112 cpm, eight times greater than the average background recording.

Discussion

Blumenkranz *et al.* demonstrated that rabbit conjunctival fibroblast proliferation can be inhibited by

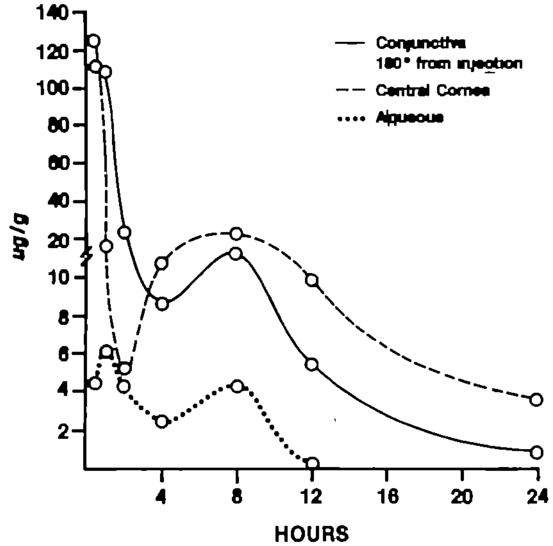

Fig. 1 *Graphic representation of the 5-fluorouracil levels obtained in conjunctiva, cornea, and aqueous following a 5 mg subconjunctival injection. The two peak concentrations seen in each tissue are consistent with a biphasic release of the 5-fluorouracil from the liposomal matrix*

50% at a 0·2 μg/l concentration of 5-fluorouracil in vitro.[1] In the present study this concentration was found in conjunctiva, cornea, and sclera 96 hours after a single injection, and in aqueous for more than 12 hours. Graphic representation (Fig. 1) demonstrates a biphasic release, with peak concentrations at 30 to 60 minutes and four to eight hours in all specimens. This is consistent with the release of separate fractions of incorporated and unincorporated 5-fluorouracil within the liposomal matrix. Electron microscopy of the liposomes following subconjunctival injection supports this hypothesis.[7] Over the first eight hours the liposomes are shown to lose their configuration with the release of the bound drug.

The ideal delivery system would provide a high, prolonged concentration of 5-fluorouracil in the subconjunctival tissues overlying the filtering site, with low concentrations of 5-fluorouracil in the other ocular tissues. This would promote an antifibrotic effect at the surgical site while minimising the toxic effects elsewhere in the eye. Comparison of peak levels obtained by this liposomal delivery system with those obtained in previous studies where 5-fluorouracil was administered either by subconjunctival injection[8,9] or by topical drops[5] suggest that a lower peak concentration was obtained in aqueous (Table 3) and in all ocular tissues examined except for the conjunctiva overlying the liposomal injection site (Table 4).

Table 3 *Peak aqueous levels of 5-fluorouracil with various delivery methods*

	μg/g
Subconjunctival liposomal 5-fluorouracil (10 mg)	12·0
Topical 5-fluorouracil (7·2 mg)[5]	199·6
Subconjunctival 5-fluorouracil (10·5 mg)[8]	29 4

Table 4 *Peak ocular levels of 5-fluorouracil by various delivery methods*

	Subconjunctival liposomal 5-fluorouracil (10 0 mg)	*Topical 5-fluorouracil[5] (7 2 mg)*	*Subconjunctival 5-fluorouracil[9] (12·5 mg)*
Cornea	226 0 μg/g	502 9 μg/g	457 6 μg/g
Lens	3 1 μg/g	6 2 μg/g	NA
Conjunctiva	106 0 μg/g	589·8 μg/g	NA

NA = not available

On the other hand high levels of 5-fluorouracil in the sclera and conjunctiva located at the injection site were obtained throughout the 96 hours studied. The combination of lower peak concentrations of 5-fluorouracil in the cornea and aqueous and high concentrations of 5-fluorouracil surrounding the subconjunctival injection site may have important clinical implications for the efficacy of this delivery system and for the placing of the liposomal matrix in relation to the filtering site.

In the analysis of the results of this study the levels of 5-fluorouracil found may have been elevated artificially as a result of simultaneous binocular injections. Rootman *et al.* have demonstrated aqueous levels of 5-fluorouracil in the contralateral eye following subconjunctival injection to be 3·7% of those found in the injected eye at peak concentration.[10] As a result the effect of binocular injections on the levels obtained is probably small and is insignificant for future extrapolation in clinical studies.

This preliminary investigation demonstrates the possible applicability of liposomes to improving the delivery of 5-fluorouracil in glaucoma filtering surgery. The ability to prolong the scleral and conjunctival concentrations while reducing the peak ocular concentrations of 5-fluorouracil as shown in this study may prove beneficial to the success of surgery and the avoidance of secondary ocular toxicity. Future studies will be necessary to determine the effectiveness of the liposomal 5-fluorouracil to control fibroblast proliferation and inhibit bleb failure in comparison with standard therapy and 5-fluorouracil alone.

The authors have no commercial or proprietory interest in this liposomal delivery system and have received no financial support in performing this investigation

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Vitrectomy for idiopathic epiretinal membranes causing macular pucker

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SUMMARY We used vitreous surgery to remove idiopathic epiretinal membranes from the macular area in 70 consecutive cases. The abnormal tissue was successfully removed in each case. Vision improved postoperatively in 61 eyes (87%), remained unchanged in six eyes (9%), and worsened in three eyes (4%). However, at the time of final examination vision was improved in only 47 eyes (67%), primarily because of the occurrence or progression of nuclear sclerosis, which occurred in 38 of 60 phakic eyes (63%). Four preoperative factors were associated with final visual acuity of 20/60 or better: (1) initial vision of 20/100 or better, (2) shorter preoperative duration of blurred vision, (3) thin epiretinal membrane, and (4) absence of traction retinal detachment.

Localised epiretinal membranes may occur in the posterior pole of eyes without any associated retinal disease. Membranes may rarely be congenital or developmental, but more often they are acquired Idiopathic epiretinal membranes can cause reduced vision and metamorphopsia by several mechanisms, including tissue covering and/or distorting the macula; low traction retinal detachment of the posterior pole; vascular leakage with intraretinal oedema; and obstruction of axoplasmic flow.[1]

Vitreous surgery is now used to remove the epiretinal tissue in selected cases. This paper reviews our experience treating 70 consecutive cases of idiopathic epiretinal membranes causing macular pucker and identifies prognostic factors for good postoperative visual acuity.

Material and methods

We retrospectively reviewed the records of 70 consecutive cases of idiopathic epiretinal membranes treated by vitrectomy and removal of epiretinal tissue from the macula. The term 'idiopathic' referred to epiretinal membranes occurring in the absence of any known vitreoretinal disease or pathology except for posterior vitreous detachment; therefore eyes with peripheral retinal tears were excluded. Patients under 40 years old were also excluded because such cases are sometimes considered to be congenital or developmental, though we believe they are usually acquired.[2]

There were 34 males and 36 females. The patients' ages ranged from 42 to 85 years (median 68 years, mean 67 years). The right eye was involved in 37 cases and the left in 33. The preoperative vision ranged from 20/50 to hand motion at 1·5 m (5 feet). Five eyes were aphakic before vitrectomy and five other eyes had an intraocular lens. The follow-up interval ranged from 6 months to 65 months (median 12 months, mean 14 months). The vitrectomy techniques used to treat these cases have been previously published.[1,3-5]

For each case 49 factors related to the preoperative examination, 38 factors relating to the operative procedure, and 23 factors related to the postoperative examination were tabulated. Items recorded for the history included age, sex, duration of blurred vision, duration of metamorphopsia, and types of previous ocular surgery. Findings from the preoperative examination included right or left eye, visual acuity, type of any lens opacity, aphakia or pseudophakia, intraocular pressure, vitreous opacity, posterior vitreous separation, type of epiretinal membrane (thin or more substantial), pigmentation

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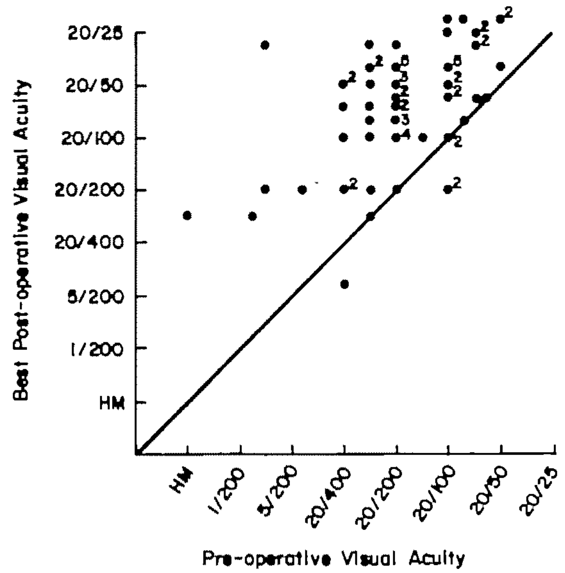

Fig 1 *Scattergram showing the preoperative visual acuity plotted against the best postoperative visual acuity HM=hand motion Numbers adjacent to dots represent the number of eyes present at a specific location Absent numbers imply a single eye at that particular location on the graph. Dots above and to the left of the diagonal represent eyes with improved vision, dots below and to the right of the diagonal represent eyes with worse postoperative vision, and dots on the diagonal represent eyes with unchanged vision. Most eyes had improved vision after surgery.*

of the epiretinal membrane, elevation of an edge of the epiretinal membrane, retinal vascular distortion, retinal striae, retinal dragging, presence of traction retinal detachment, macular thickening and/or cystoid macular oedema visible by slit lamp biomicroscopy, and epiretinal membrane in the fellow eye

A statistical analysis was performed to determine which of the preoperative and intraoperative factors were associated with final visual acuity of 20/60 or better. All comparisons of proportions were done by χ^2 tests. The Mann-Whitney U test was used to compare duration of symptoms between groups.

Results

The epiretinal membrane was removed from the fovea at the time of vitrectomy in all cases. However, in 28 eyes (40%) remnants of the epiretinal membrane were left posterior to the equator. In three eyes (4%) fragments of the epiretinal membranes were left in the macula. Mild petechial haemorrhages occurred at the time of surgery in 16 eyes (23%).

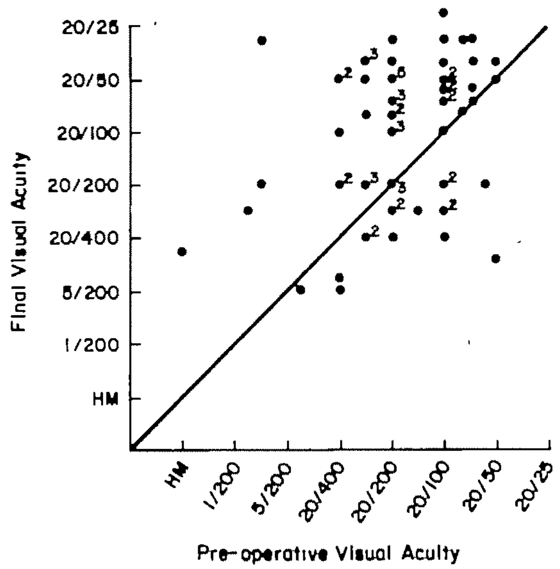

Fig 2 *Scattergram showing the preoperative visual acuity plotted against the final visual acuity With longer follow-up fewer patients had improved vision after surgery, and more patients had worse vision. (Compare with Fig 1, and see Fig 3 for more details about subsequent visual loss).*

Postoperatively the vision improved in 61 eyes (87%) and remained the same in six eyes (9%) (Fig. 1). Three eyes had worse vision after surgery. At the time of final examination the vision was improved in 47 eyes (67%), worse in 16 eyes (23%), and unchanged in seven eyes (10%) (Figs. 2 and 3). The primary reason for subsequent decrease in visual acuity was the occurrence or progression of nuclear sclerosis of the crystalline lens. This occurred in 38 (63%) of the 60 phakic eyes. Of the 14 eyes with decreased final visual acuity 11 (79%) had development or progression of nuclear sclerosis. The median time for best postoperative vision was six months, whereas the median time for final vision was 12 months. There was no difference in the length of

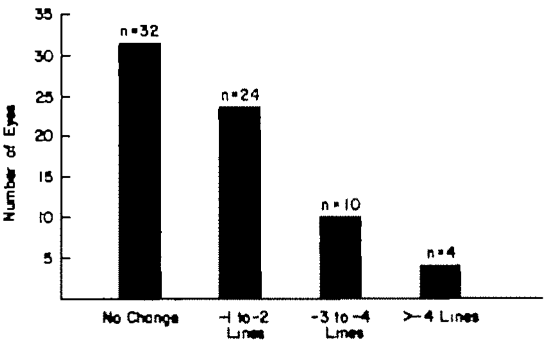

Fig 3 *Difference between best postoperative and final postoperative visual acuity in number of lines The most common reason for subsequent visual loss is the occurrence or progression of nuclear sclerotic cataracts*

follow-up between those patients whose vision improved and those that worsened.

Four preoperative factors were associated with a final visual acuity of 20/60 or better: initial visual acuity of 20/100 or better, shorter duration of blurred vision, thin epiretinal membrane, and absence of traction retinal detachment (Table 1).

A complete posterior vitreous detachment, as determined from the preoperative examination and/or intraoperative findings, was present in 55 eyes (79%). Seven eyes (10%) had no posterior vitreous detachment. The remaining eight eyes had a partial posterior vitreous detachment. In six eyes the posterior vitreous was partially attached to the epiretinal membrane.

The epiretinal membrane had a thin, cellophane-like appearance in 39 eyes (56%), and it was thicker in 31 eyes (44%). In 43 eyes (61%) a partly raised edge was visible preoperatively. Twelve eyes (17%) had various degrees of cystoid macular oedema visible preoperatively by contact lens examination. Fluorescein angiography was not routinely performed. Eleven eyes (16%) had an epiretinal membrane of less severity involving the macula in the fellow eye.

COMPLICATIONS

Peripheral retinal tears were identified at the end of the operation in four eyes (6%). These were treated by cryotherapy, partial fluid/air exchange, and postoperative face-down positioning. One eye developed a peripheral retinal detachment postoperatively, and it was successfully treated with a scleral buckling procedure. No posterior retinal breaks occurred during removal of the epiretinal membranes.

Angle closure glaucoma occurred postoperatively in one eye. It was treated with a laser iridotomy. Progressive nuclear sclerotic lens changes developed in 38 (63%) of 60 phakic eyes. The causes of this complication are unknown, and it is being investigated further. At the time of final examination recurrent epiretinal membranes affecting the macula were found in three eyes (4%). There was no apparent reason for the recurrence of epiretinal membranes in these three eyes.

Discussion

Idiopathic epiretinal membranes causing macular pucker and impaired vision are a well known acquired clinical condition. Vitreous surgery is now used to remove the epiretinal membrane from the macular area in selected cases if there is substantial visual loss. However, visual recovery is usually incomplete. There are no firm criteria for recommending surgery, and the indications may vary depending on the visual needs of each patient. However, most of the cases (84%) in our series had preoperative visual acuity of 20/100 or worse in the involved eye.

Table 1 *Vitrectomy for idiopathic macular pucker prognostic factors for final visual acuity*

Preop factor	*Final postoperative vision – number of eyes (%)*	
	≥20/60	*<20/60 (p value)*
Preop VA ≥20/100	21 (81)	5 (19) (<0·0002)*
Preop VA <20/100	18 (41)	26 (59)
Thin	26 (67)	13 (33) (<0·05)*
More substantial	12 (40)	18 (60)
TRD	2 (18)	9 (82) (<0·007)*
No TRD	37 (63)	22 (27)
Duration of blurred vision (median)	350 days	747 days (<0·001)†

VA=visual acuity.
TRD=traction retinal detachment
*p Value based on χ^2 test
†p Value based on Mann-Whitney U test

Idiopathic epiretinal membranes present a unique opportunity to study the effects of epiretinal tissue on visual function, because these eyes do not have other prior or concurrent retinal disease. Identification of prognostic indicators of visual results helps in case selection for surgery and may aid in understanding the pathogenesis of visual loss in this condition. In our series four factors were associated with final visual acuity of 20/60 or better: (1) initial visual acuity of 20/100 or better, (2) shorter duration of blurred vision, (3) thin, cellophane-like appearance of the epiretinal membrane, and (4) absence of posterior traction retinal detachment.

Relatively good initial visual acuity and shorter duration of blurred vision have also been found to be prognostic indicators of good postoperative vision after vitrectomy for other types of epiretinal membranes causing macular pucker. This probably indicates less initial macular damage.[4] Epiretinal membranes with a thin (cellophane) appearance also had a better visual prognosis. This agrees with the observations of others, though the reason for this association is not certain.[7]

In 11 cases the traction caused by the epiretinal tissue produced a limited low retinal detachment. This correlated with a poorer visual result, probably because of further disturbance of the retinal architecture and interference with the retinal pigment epithelium-photoreceptor complex.

Peripheral retinal tears were found at the end of surgery in four eyes (6%). These were successfully treated by cryotherapy and partial fluid/air exchange. This underscores the need for careful examination of the peripheral retina by indirect ophthalmoscopy with scleral depression at the end of the operation.

The high incidence of progressive postoperative nuclear sclerosis found in this series is of obscure aetiology. Michels had previously reported an incidence of 34% in 90 cases.[8] Many reasons could explain the higher incidence of postoperative nuclear sclerosis in this series, including longer follow-up and selection of homogeneous cases of epiretinal membranes as compared with the previous series of mixed aetiology. Margherio *et al.*[9] attribute their lower incidence of postoperative nuclear sclerosis (12·5%) to a variety of factors, including shorter operating time, distance of infusion port from the lens, type of irrigating fluid, and different surgical techniques, leaving anterior vitreous behind the lens. Recently, however, McDonald *et al.*[10] using similar surgical techniques, observed this complication in 39% of their cases. Clearly the postoperative occurrence of nuclear sclerosis deserves further study. It is being investigated further.

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Corneal shape and astigmatism: with a note on myopia

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SUMMARY The elliptical shape and the physiological astigmatism of the normal neonatal human cornea are attributed to the ellipsoidal shape of the eyeball. This in turn is a feature of ocular development. The analysis is used to examine earlier observations on myopia.

The human eye is said to be spherical, the cornea circular, and corneal astigmatism unexplained.[1] However, careful measurements show that the eyeball is oblate[2,3] and the cornea elliptical.[4] The object of this paper is to try to advance an explanation of these observations.

This analysis asks whether the shape of the young cornea depends on that of the eyeball as a whole. The initial prospect of success is barely encouraging. The neonatal eyeball has a radius of about 8·25 mm, whereas the radius of corneal curvature is nearer 7·4 mm. The disparity increases with age from 10% to some 27% in the adult eye. The fully developed eye therefore has grafted on it, as it were, a refractive bubble of greater curvature than its own, which satisfies well-known optical requirements.

However, heterotropic surface forces—for example, those due to the action of the recti muscles — are transmitted to the cornea via the sclera.[5] The corneal fibrillar organisation (of the adult eye) is not random but polarised, as though the cornea were subject to lines of force, orthogonal to each other and in line with the muscular directions of action, giving rise to an outline reminiscent of a Maltese cross.[6]

Moreover, the cornea barely grows after birth, and it increases its radius of curvature later only by an equivalent of less than 4 D, compensating optically therefore only for some 22% of the postnatal growth (about 6 mm) of the ocular axis. It would seem, therefore, that, approximately up to term, the cornea grows and develops in step with the rest of the eye but resists the effects of ocular growth after birth more and more effectively.

However, in two senses it is deformed already at birth. On average its refraction is slightly aspherical and its shape non-circular. A priori it is improbable that it should develop these characteristics—which are found in many mammals—actively by endogenous forces. Can it do so passively?

Hypothesis

While various authors agree that the vertical diameter of the globe is the smallest, there is some uncertainty as regards which is the largest. So far only the sagittal diameter has been measured in situ; enucleated material tends to be flaccid, and measurements may depend in part on the resting orientation of the eyeball. In the embryo Scammon and Armstrong[7] found the sagittal diameter to be the largest, while others[3] give its value as intermediate to the other two. Ethnic differences may have a role.[8] It will be shown that the above uncertainty as regards the relative ocular dimensions is immaterial in the present context so long as the vertical diameter is the smallest. The oblate shape of the eyeball is due to embryonic development. Lešer[9] showed that, even at the 5–6 mm stage, the human eye is tubular, a circumstance attributable to ectodermal growth. More recent work[10] concurs with this.

The present postulate is that both corneal ellipticity and physiological (with-the-rule) astigmatism are attributable to the oblate form of the fetal eye, a hypothesis supported inter alia by the observation that the young cornea yields less to stress than does the sclera.[11]

If, then, the corneal dimensions differ in the two principal meridians, are there external forces to account for this? Similarly, if the curvatures differ in the two meridians, are there external forces to achieve this? More especially, if the answer to both questions is yes, are the forces related?

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Theory

SHAPE

Let the sagittal, transverse, and vertical diameters of the globe be 2a, 2c, and 2b, in decreasing order. As long as 2b is the smallest, the general conclusions of this analysis are unaffected by the relative magnitudes of the other two. As the scleral thickness is about 1/30 of the above diameters, the tension T can be estimated on the assumption that the eyeball maintains its shape under the influence of the intraocular pressure p. We follow the usual convention, namely that T, measured in a surface per unit length, acts in a direction perpendicularly to the surface. This requires a knowledge of the radius of curvature at the point of action if the surface is curved. An ellipse with principal semiaxes a and b is described by the expression

$$(x/a)^2+(y/b)^2=1 \quad \ldots \ldots \ldots \ldots \ldots \quad (1)$$

The radius of curvature at the point x=±a, y=0 equals b^2/a; similarly, at x=0, y=±b, the value is a^2/b.[12]

Although the tension T is assumed to be constant for the sclera, but may possibly differ for the cornea and almost certainly does so in the lamina cribrosa, these non-uniformities will be assumed to be negligible.

Elementary theory shows that, in any one meridian, p=T/R, where R is the radius of curvature at the point under consideration.[13] At the point of intersection of two principal meridians, the respective values being R(1) and R(2), $p=T[1/R(1)+1/R(2)]$. Let the sagittal circumference of the eyeball be described by an ellipse with semiaxes a, b (where 2a is the axial length), and the horizontal circumference by one with semiaxes a, c. Hence the pressures perpendicular to the optic axis are

$$\left.\begin{array}{ll}\text{in the vertical:} & T.b.\,(1/a^2+1/c^2)\\ \text{in the horizontal} & T.c.\,(1/b^2+1/a^2)\end{array}\right\} \quad \ldots\ldots\ldots\ldots \quad (2)$$

The ratio of the meridional areas perpendicular to them is b/c, so that the ratio G of the forces acting in the vertical and horizontal directions respectively is approximately

$$G=\left(\frac{b}{c}\right)^2\cdot\frac{a^2+c^2}{a^2+b^2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

This expression demonstrates the validity of the argument regarding 2b being the smallest ocular axis, as mentioned above. Let the numerator and denominator of the second of the two fractions be divided by c^2, and $(a/c)^2$ set equal to X; then

$$G=[1+X]/[1+X/(b/c)^2],$$

which must be smaller than unity irrespectively of the value of X.

Table 1 *Neonatal ocular dimensions and comparison between computed and observed corneal shapes*

Ocular dimensions in mm	*Caucasian*	*Japanese*
a	8·55	8·3
b	8·1	8·0
c	8·4	8·5
G (calculated)	0·963	0·941
G (observed, n=3)	0·94±0·027	

Table 2 *Calculated and observed values for neonatal astigmatism with-the-rule (in dioptres)*

	Caucasian	*Japanese*
Calculated	3·5	5·8
Observed	<4·0	2·2 (average)

The forces stretch the eyeball differently in the two directions perpendicular to the optic axis and, in so far as they are transmitted to the corneal limbus, the pull on the developing cornea in the vertical is smaller than in the horizontal. On the simplest of assumptions it follows that G is approximately equal to the ratio of the vertical and horizontal dimensions of the neonate cornea, as mentioned above. Sets of relevant data are available for Caucasian and Japanese eyes for testing equation 3. The distinction may be material, because there are significant anatomical differences between Mongol and Caucasian eyes.[14] The Caucasian[8] and Japanese[3] data are shown in Table 1 together with the calculated value of G (equation 3) and an estimate of observed values of the corneal shape ratio.

It has to be remembered, however, that the observed value is obtained for instance from photographs, that is, for a fronto-parallel plane, whereas the data are calculated 'in the round'. The ratio of the projections of the vertical and horizontal diameters of the cornea equals b/c, the values for the two populations being 0·964 and 0·941 respectively. These are similar to the calculated figures for G given in Table 1, and justify the mode of comparison of the ratio of the principal corneal dimensions and that of their projections in a fronto-parallel plane.

PHYSIOLOGICAL ASTIGMATISM

Within rather wide limits neonatal astigmatism of the cornea[15 16] is also explicable in terms of the oblate shape of the eyeball. The expression for the radius of curvature of an ellipse shows that the ratio of the two principal radii of curvature R(1) and R(2) at the anterior ocular pole is $(b/c)^2$. Given the expression for astigmatism in terms of the difference between the dioptric powers in the two principal meridians

$$\Delta P = P(1) - P(2) = (\mu - 1).[1/R(1) - 1/R(2)] \approx \{(\mu - 1)/P\}.[P(2)/P(1) - 1] \ldots\ldots \quad (4)$$

where R is the mean neonate radius of curvature ($\approx 7{\cdot}4$ mm, see Weale[8]). It is, in effect, equal to $0{\cdot}5[R(1)+R(2)]$, but no significant error is introduced by putting $R \approx R(1) \approx R(2)$. With $\mu = 1{\cdot}372$, and values culled from Table 1, those shown in Table 2 are obtained and compared with experimental ones.[16 17]

Half these values are referred to as spherical equivalents.[18] The agreement between theory and experiment is circumscribed. The large theoretical value for Japanese eyes is evidently due to the small value of $(b/c)^2$ (Table 1). Although the excised eyes from which measurements were obtained were fixed prior to measurement, no attempt appears to have been made to establish whether the inherently flaccid tissue was deformed, for example, while it hardened.

Discussion and relevance to myopia

The comparison between observed and calculated values both for corneal shape and physiological astigmatism suggests that, at least in the fetal eye, the relative deformation of the cornea is explicable in terms of tensile forces in the ocular globe. In the adult eye the transmission of such forces seems to be reduced, but this may be less valid for the myopic eye, which incidentally may have a thin sclera. The idea has been advanced[19] that the myopic eye tends to manifest compensatory features: the cornea flattening and, in a manner which was not clear to those authors, the lens too being poised to counteract myopia.

If one disregards corneal astigmatism and recalls that the myopic eye is frequently axially extended, then it is possible to estimate the condition in which the cornea will oppose myopia. Assume that the optic axis of the myopic eye is $2a'$ and its diameter $2b'$. Then it follows from equation 4 that the difference in refractive power between the myopic and the emmetropic cornea will be approximately

$$\Delta P = \{(\mu - 1)/R\}.[(b'/b)^2.(a/a') - 1] \quad \ldots\ldots\,.\,. \quad (5)$$

where $R \approx 8$ mm; $\Delta P = 0$ when $(b'/b)^2 = a'/a$. Since $a' = a(1+\eta)$ and $b' = (1+\varepsilon)$, where η and ε are small as compared with unity, the transverse diameter need increase by only one half the axial increase. As the elasticity of the cornea resists the bending forces of the globe, the geometrical change may not wholly reflect optical necessity. But it is not hard to see that an extension of the transverse diameter can also act on the lens.

Put at its simplest, owing to zonular tension the focal length f of the lens is proportional to b or $f = kb$. Thus in the emmetropic eye, $f = 50$ mm, so that $50 = 11\ k$, b in emmetropia equalling approximately 11 mm. Therefore $f = 4{\cdot}55\ b$. An increase in b to b′ by only 1 mm in myopia[1] hence leads to a reduction in lenticular power of over 1·5 D, that is, myopia is counteracted. The calculation is invalidated for an ovoid eye, as when a staphyloma develops, but for the majority of simple myopes it offers at least a qualitative explanation of the earlier observations.[19]

The aetiology of myopia is still not understood. However, in so far as axial elongation is involved, this must be the result of the action of some force(s). Ocular inflation could play a part in teenage myopia as it does in the developing eye.[20] It is important to determine to what extent mechanical factors as distinct from growth may be involved at this later age.

In summary, a consideration of the tensile forces acting on the surface of the ocular globe helps our understanding of the development of corneal shape and curvature and may point to a possible modification of some of the processes causing myopia.

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Addition of hyaluronidase to lignocaine with adrenaline for retrobulbar anaesthesia in the surgery of senile cataract

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SUMMARY A double-blind trial demonstrates the effectiveness of adding hyaluronidase to lignocaine with adrenaline in producing ocular akinesia and anaesthesia in retrobulbar nerve blocks. 92% of the blocks in which hyaluronidase was used for intracapsular cataract surgery were judged successful compared with 56% of those without added hyaluronidase ($p<0 \cdot 01$).

Hyaluronidase is an enzyme which depolymerises the polysaccharide hyaluronic acid present in the intracellular matrix of connective tissue.[1] It increases the spread of locally injected anaesthetics and so should improve the effectiveness of nerve blocks.

Reports on its value in retrobulbar anaesthesia have differed. Atkinson[2] and Lebensohn[3] found it to be useful, while Mindel[4] did not find it to be effective. Dissatisfaction with the initial success rate of lignocaine with adrenaline alone prompted this trial with the addition of hyaluronidase to the anaesthetic.

Materials and method

One hundred and fifty consecutive patients admitted for senile cataract surgery were randomly allocated to one of two groups, A or B. Two identical 150 ml bottles of local anaesthetic were prepared. To each bottle was added 100 ml of 2% lignocaine and 1 ml of adrenaline 1/1000. To one of the bottles 1500 IU of hyaluronidase was added. One bottle therefore contained 100 ml of 2% lignocaine with adrenaline 1/100 000 and other 100 ml 2% lignocaine with adrenaline 1/100 000 and 15 IU hyaluronidase/ml.

The bottles were labelled A and B by an independent observer who was told which bottle contained the hyaluronidase. After the labelling of the bottles only the observer knew what was in each bottle. The same procedure was repeated when more anaesthetic was needed. The code was broken at the end of the series of 150 patients.

Since no trouble had been previously experienced with facial nerve blocks, only 2% lignocaine with adrenaline 1/100 000 (prepared separately) was used for this procedure. A combined van Lint and O'Brien technique is used routinely, with 1 ml injected over the mandible 2·5 cm in front of the ear lobe and 2·5 ml injected above and below the orbital rim, the injection being started 2·5 cm lateral to the orbital rim.

The retrobulbar injection was 2 ml given through a 26 G 50 mm needle. The injection was started at the lower, lateral orbital margin, the needle passed straight back through the skin of the lower lid for 1 cm to go through the orbital septum, and then angled at 45° to follow the lateral wall of the orbit to the apex. An attempt was made to place the anaesthetic solution within the muscle cone.

Preoperative sedation was 25 mg chlorpromazine given orally approximately half an hour before surgery. No local anaesthetic drops were put in the eye either before or during the operation.

Six patients were operated on at each session. All anaesthetics were given by me at the start of each session and before scrubbing up for surgery. The first patient to be operated on therefore had his local anaesthetic about 15 minutes before surgery (10 minutes to give six anaesthetics plus 5 minutes for scrubbing up) and the last patient about one hour and five minutes after the local anaesthetic, an average of 10 minutes being allowed for each operation. This time gap is well within the normal range given for the duration of lignocaine with adrenaline.[5] The addition of hyaluronidase has been shown not to reduce this duration.[6]

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The patients were operated on in the order in which they presented at the outpatients department and were given anaesthetic A or B alternately. No attempt was made to time the onset of akinesia or anaesthesia. Akinesia and anaesthesia were assessed on the operating table by me immediately before surgery and after the eye had been washed and draped. The following grading system was used:

Grade 1. Complete akinesia and anaesthesia as shown by (*a*) painless insertion of the upper lid suture; (*b*) Complete absence of eye movements; (*c*) the eye in the primary position; (*d*) complete anaesthesia of conjunctiva and cornea.

Grade 2. Akinesia and anaesthesia considered adequate for safe intraocular surgery as shown by (*a*) painless insertion of upper lid suture; (*b*) eye movements less than 15° (estimated) in any direction of gaze; (*c*) complete anaesthesia of conjunctiva and cornea.

Grade 3. Unsuccessful akinesia and anaesthesia as judged by (*a*) painful insertion of the upper lid suture; (*b*) eye movements greater than 15° (estimated) in any direction of gaze.

Patients with a grade 3 anaesthetic had a repeat retrobulbar injection of 2% lignocaine with adrenaline 1/100 000.

The surgical procedure consisted of (1) a 3/0 silk suture passed through the central upper lid margin and clipped with mosquito forceps to retract the lid; (2) a Graefe knife section; (3) a peripheral iridectomy; (4) one preplaced 8/0 silk suture; (5) intracapsular cryoextraction of the lens; (6) two further 8/0 corneoscleral sutures. A superior rectus suture for eye fixation was not used.

Three patients had a retrobulbar haemorrhage and were excluded from that particular session but re-entered the trial with the same anaesthetic when they were rescheduled for surgery one week later. All preoperative tensions were less than 21 mmHg Schiøtz.

Results

The results were analysed by χ^2 test with one degree of freedom.

A successful anaesthetic was grade 1 or grade 2. Of the 150 blocks 74% were successful first time, with the remainder needing a second retrobulbar injection. Of the 75 who had added hyaluronidase 92% were successful compared with only 56% of those without hyaluronidase ($p<0{\cdot}01$) (Table 1).

Sixty-seven of the 150 anaesthetics were grade 1 and nearly three-quarters of them had added hyaluronidase. Conversely nearly 80% of the 39 anaesthetic failures were in patients without added hyaluronidase ($p<0{\cdot}01$). The 44 grade 2 anaesthetics were more or less equally divided between the two groups (Table 2).

Table 1 *Success and failure rate of anaesthesia in all patients and in those with added hyaluronidase and those without*

	Success (%)	*Failure (%)*	*Total (%)*
All anaesthetics	111 (74)	39 (26)	150 (100)
With hyaluronidase	69 (92)	6 (8)	75 (100)
Without hyaluronidase	42 (56)	33 (44)	75 (100)

Table 2 *Grade of anaesthesia achieved in patients with added hyaluronidase and without hyaluronidase*

Grade of anaesthesia	*With (%) hyaluronidase*	*Without (%) hyaluronidase*	*Total (%)*
1	48 (72)	19 (28)	67 (100)
2	21 (48)	23 (52)	44 (100)
3	6 (15)	33 (85)	39 (100)
Total	75	75	150

Table 3 *Patients with vitreous 'loss' related to grade and type of anaesthesia*

Grade of anaesthesia	*Without hyaluronidase*	*With hyaluronidase*	*Total*
Grade 1	0	1	1
Grade 2	1	0	1
Grade 3	4	1	5
Total	5	2	7

COMPLICATIONS

Seven patients (4·6%) had prolapse of vitreous into the anterior chamber at the time of surgery. Five of those were in patients not given hyaluronidase and two in those who had added hyaluronidase. The difference is not statistically significant ($0{\cdot}2<p<0{\cdot}5$) (Table 3).

A larger series might show a difference, since it is my experience that vitreous prolapse is nearly always associated either with poor anaesthesia or with repeated retrobulbar injections. Repeated injections of fluid into the retrobulbar space will increase the pressure behind the eye in a manner analagous to that of a small retrobulbar haemorrhage. When the eye is opened and the intraocular pressure falls to zero, the effect of increased pressure behind the eye will be to push forward the vitreous in response to the pressure gradient created.

Twenty-one (14%) patients had accidental rupture of the anterior lens capsule necessitating extracapsular lens extraction. Of those, 11 (52·4%) were in patients without added hyaluronidase and 10 (47·6%) were in the group with hyaluronidase. The difference is not statistically significant.

Discussion

Hyaluronidase has been used as an adjunct to local anaesthesia since the late 1940s. It found favour with ophthalmologists and continues to do so (Christy NE, personal communication) despite Mindel's negative report in 1978.[4] In his 27 cases there was a 25% failure rate without hyaluronidase and a 50% failure rate with hyaluronidase. Mindel, however, did not add adrenaline to his anaesthetic, so his results are what one might have predicted. Without adrenaline to restrict absorption the hyaluronidase acted only to increase diffusion, so limiting its effectiveness. He did find that the induction of anaesthesia was faster with hyaluronidase, which would be expected from the more rapid initial spread of the anaesthetic produced by the hyaluronidase.

Good local anaesthesia in cataract surgery is almost a sine qua non for good results. To operate on an eye which has perfect akinesia and anaesthesia is a relatively simple procedure, with a few complications and an excellent prognosis. To operate on an incompletely anaesthetised eye is an invitation to disaster.

Some practitioners are doubtless more adept than others at placing their retrobulbar injections exactly within the muscle cone. Oji and Oji got 73% absolute akinesia with lignocaine alone in their series of 30 patients and 93% of 30 patients with a mixture of lignocaine and bupivacaine.[7] For those of us less skilled the addition of hyaluronidase probably allows for an error of 1 cm in the placement of the anaesthetic.[6]

CONCLUSION

I recommend the addition of 15 IU hyaluronidase/ml to 2% lignocaine with adrenaline 1/100 000 for retrobulbar blocks as an aid to achieving complete ocular akinesia and anaesthesia in cataract surgery.

I am grateful to Mrs Joanna Thomson for recording the results and to the Zimbabwe Council for the Blind, Christoffel Blindenmission, and the Royal Commonwealth Society for the Blind, who provide the financial support for Norton Eye Unit

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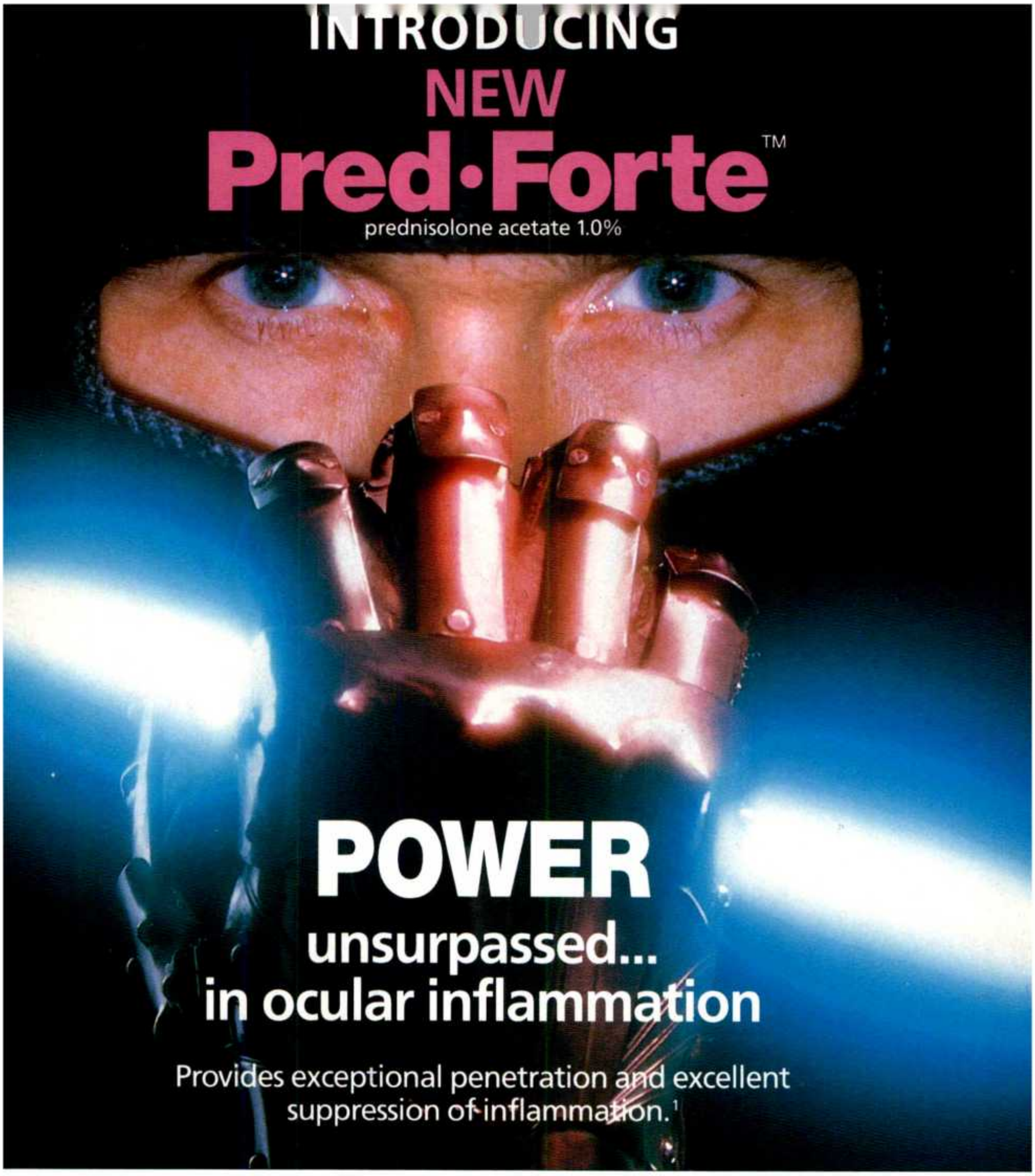
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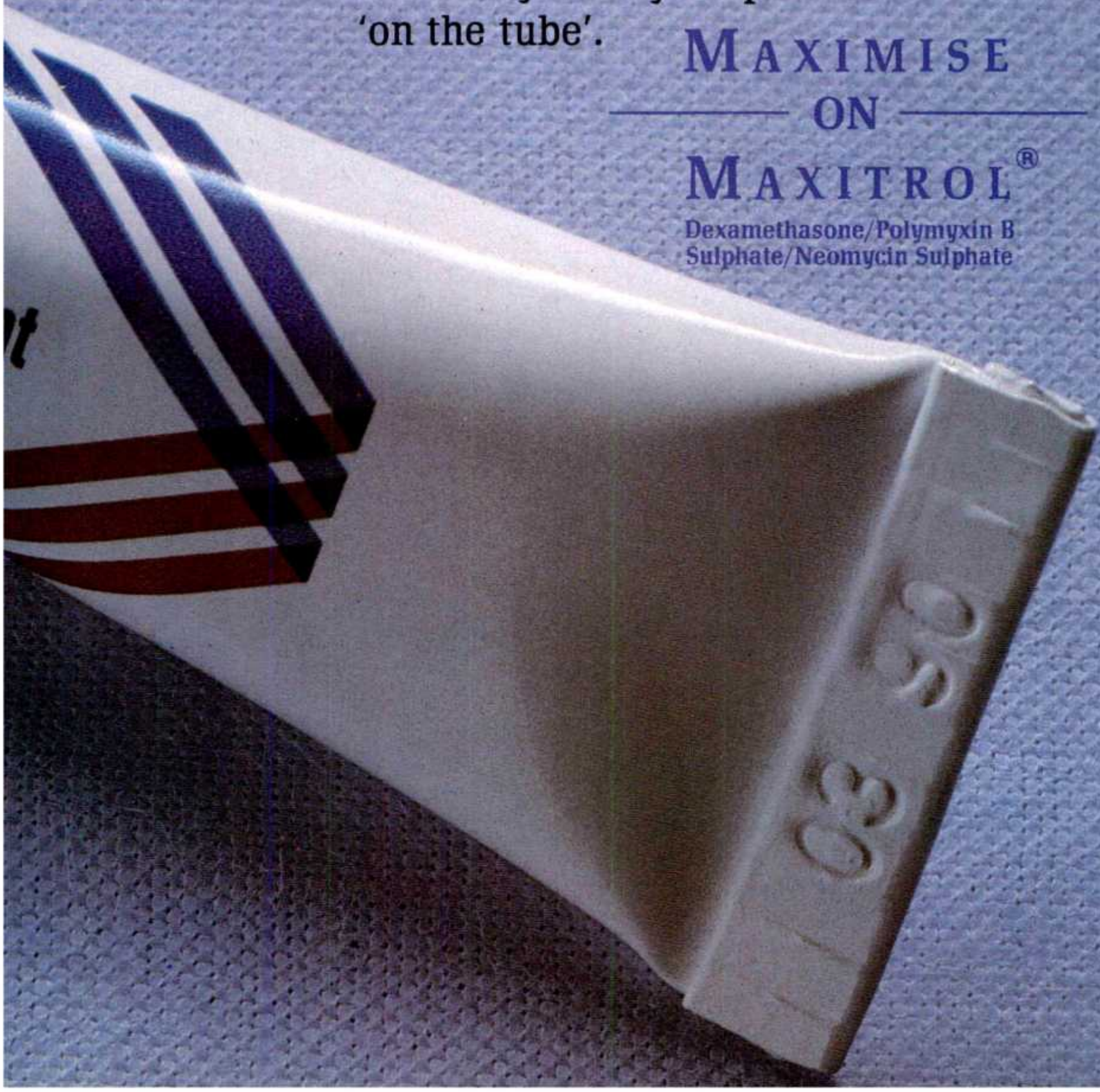

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Clinical assessment of retinal elevations: a review of methods and a novel clinical technique*

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SUMMARY A new clinical test for the detection of retinal elevation is described. The test, based on alterations of retinal surface light reflexes during indirect ophthalmoscopy, is extremely sensitive to very shallow detachments. The optics, the degree of sensitivity, and the limitations of the new clinical technique are examined and other clinical methods are reviewed.

The assessment of retinal disease is largely based on ophthalmoscopic signs and on auxiliary tests of retinal function, such as tests of visual field, colour discrimination, or retinal electrophysiology, and of anatomical and functional relationships—for example, fluorescein angiography, ultrasonography, and computerised *x*-ray tomography Whereas extremely shallow retinal elevation (beyond the resolution of binocular indirect ophthalmoscopy) can often be inferred from other clinical signs—for example, the presence of subretinal haemorrhage or turbid fluid—in some instances it is necessary to assess the degree of elevation by clear subretinal fluids. It is with respect to the latter group that this paper is particularly addressed.

Systematic review of the clinical techniques available for assessing retinal elevation

The direct ophthalmoscope was introduced in 1851 by von Helmholtz,[1] although the principles of the technique, as detailed by Purkinje,[2] predate the advent of this instrument by several years. Indirect ophthalmoscopy was described by Reute in 1852[3] and a binocular instrument was soon to follow in 1861.[4] Binocular indirect ophthalmoscopy did not, however, gain widespread use until the introduction of the head mounted ophthalmoscope by Schepens in 1947.[5] Slit-lamp biomicroscopic examination of the fundus was possible (in all except eyes with extreme myopia) only after the introduction of the corneal contact lens, the high power concave lens (Hruby lens), or the high power biconvex lenses of good optical quality (namely the +60 dioptre and, more recently, the +90 dioptre).

Irrespective of the method of examination used, the techniques of optical assessment of retinal elevations can be considered in two groups. The first group of methods assess the degree of separation of retinal features from the normally adjacent retinal pigment epithelium and choroid. The less used second group depend on alterations of surface contour that occur with elevations of the sensory retina.

METHODS DEPENDENT ON SEPARATION OF IMAGES

The central displacement of the retinal structures or associated lesions—for example, retinal haemorrhages or holes—with respect to the underlying choroid and retinal pigment epithelium provides an optically assessable measure of retinal elevation. There are several methods of examining this displacement:

Monocular methods. (1) Disparity of dioptric correction required to focus the retinal and the choroidal details during direct ophthalmoscopy; (2) variable and increasingly hypermetropic objective refraction (indirectly related to (1)); (3) parallactic movement of retinal features over the choroidal background pattern; (4) position of shadows, cast by retinal structures, on the underlying choroid; (5) examination of 'optical sections' created with the slit-lamp biomicroscope.

Binocular methods. (1) Stereoscopic binocular indirect ophthalmoscopy and its adaptation to slit-lamp biomicroscopy (with the +60 dioptre El Bayadi lens or the +90 dioptre condenser lens); (2) stereoscopic binocular slit-lamp biomicroscopy, with a contact lens or −56 dioptre Hruby lens to create upright virtual images; (3) stereoscopic pairs of fundus photographs.

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*Presented in part at Oxford Ophthalmological Congress, 1987

Correspondence to Mr G E Rose, FRCS.

In practice the direct ophthalmoscope has the advantage of permitting viewing of the fundus through a small pupil, but with the limitation of this being only a monocular view. The approximation of 3 dioptres of hypermetropia for every 1 mm of retinal elevation (2 dioptres in the aphakic eye) is well known to most ophthalmologists. With normal retinal apposition structures such as retinal vessels do not cast visible shadows on the underlying retinal pigment epithelium and choroid; to see such shadows implies an elevation of the retina. The presence of parallactic movements of retinal features with respect to the choroidal pattern is demonstrable only when the patient's pupil is dilated; uninterrupted visualisation of the retina during the side-to-side movement of the ophthalmoscope (this movement generating the parallax) is not possible with an undilated pupil.

Parallactic movement can readily be demonstrated with the binocular indirect ophthalmoscope. One method involves closure of alternate eyes of the observer (thereby mimicking monocular indirect ophthalmoscopy with an observer movement equivalent to the reduced interpupillary distance of the instrument) and the second method involves the side-to-side displacement of the observer and the condenser lens (with the option of monocular or binocular viewing). The presence and displacement of shadows cast by retinal structures is often appreciated with the indirect ophthalmoscope, both because of the strong illumination and also because of the offset between the axes of illumination and observation.

Although the slit-lamp biomicroscope is generally regarded as a binocular instrument, the oblique 'optical section' may be assessed monocularly; the viewing of an oblique optical section requires a well dilated pupil. Although mydriasis is needed for binocular indirect ophthalmoscopy, it is not necessary for the slit-lamp biomicroscope arrangement using a +90 dioptre condenser lens. In contrast, the virtual images created by the Hruby lens or contact lens during fundal examination at the slit-lamp biomicroscope can be examined stereoscopically only with good mydriasis. The fundus camera is based on the principle of indirect ophthalmoscopy and, for good quality stereo pairs or photographs, needs a well dilated pupil.

METHODS DEPENDENT ON ALTERED RETINAL SURFACE TOPOGRAPHY

Of the methods dependent on the separation of images (*vs*), only the examination of the optical section created on the slit-lamp biomicroscope draws further information from the alteration of retinal surface topography. Thus, when examining an elevation of the retina there is a deviation from the normal parallel concavities (of the retina and the choroid) as created by the oblique optical section. Depending on the degree of detachment, the retinal contour may be planar (instead of concave) or even convex with respect to the incident slit-beam illumination.

FURTHER THEORETICAL METHODS FOR ASSESSING ALTERED RETINAL SURFACE TOPOGRAPHY

The examination techniques reviewed form a powerful armamentarium for the detection of retinal elevations. They fail, however, to utilise the full potential of the changes in surface contour that occur with retinal elevation.

Although more complex in practice, the retinal surface can be considered to be a concave mirror over most of its area, and very small degrees of retinal

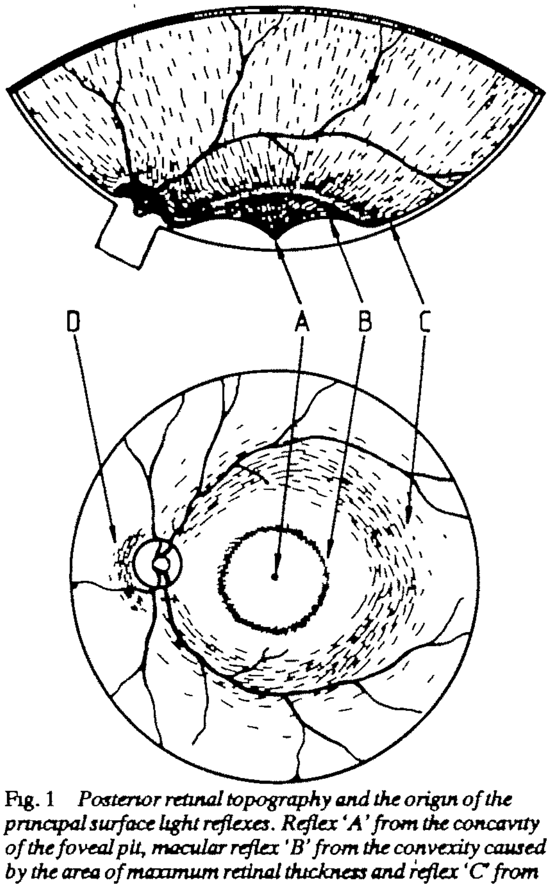

Fig. 1 *Posterior retinal topography and the origin of the principal surface light reflexes. Reflex 'A' from the concavity of the foveal pit, macular reflex 'B' from the convexity caused by the area of maximum retinal thickness and reflex 'C' from the concavity of the extramacular retina. The Weiss reflex, 'D', arises from the concavity nasal to the optic disc.*

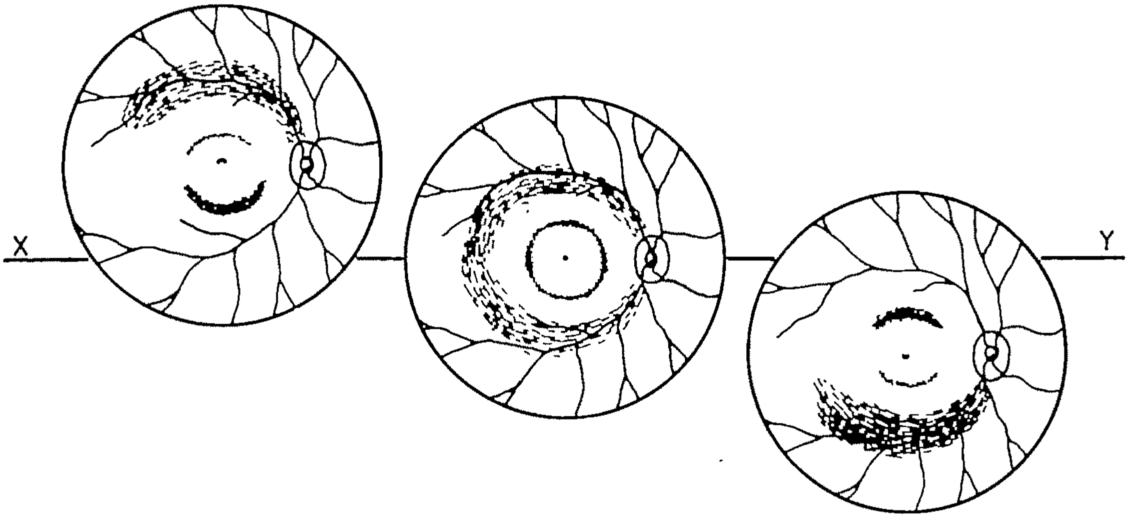

Fig. 2 *Alterations of the position of the three major light reflexes from the retinal surface with across-the-axis displacements of the condenser lens during indirect ophthalmoscopy, the light reflexes are represented by shading The line XY represents the horizontal meridian at the midpoint of the eye under examination*

detachment will produce a marked increase in the radius of curvature of this concavity. As the retinal elevation increases, so the shape changes from concave to planar and finally becomes convex. The normal retinal surface reflexes that occur during indirect ophthalmoscopy (both binocular and monocular) are predominantly those that occur at a concave mirror, retinal elevation disturbing these patterns and thereby becoming manifest on clinical examination.

The detection of aberrations from the correct concavity of a spherical or parabolic mirror is a well established technique in the construction of astronomical telescopes. The Foucault test[4] used in the detection of these aberrations is not, however, applicable as a test of retinal concavity. In contrast, the *movements* of the light reflexes during indirect ophthalmoscopy, as detailed in this paper, provide a novel, quick, and sensitive technique for the detection of shallow elevations of the sensory retina

Shifting retinal light reflexes—the new clinical technique

When the pupil is well dilated and the surface light reflexes are strong during indirect ophthalmoscopy, the technique may be modified by the movement of the condenser lens from side to side. This displacement (by only a few millimetres) of the condenser lens from the optical axis causes a marked alteration of the fundal surface light reflexes.

In the normal fundus, especially in young subjects, the light reflexes will be seen to comprise three distinct reflexes, with additional reflexes in certain cases (Fig. 1). The most peripheral conforms to a section of an annular reflex, often extending out to beyond the major temporal vascular arcades; this

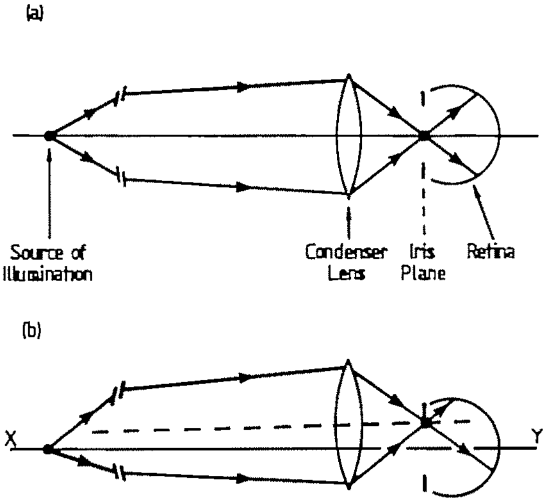

Fig. 3 (a) *Optics of the illumination of the retina under examination during indirect ophthalmoscopy and* (b) *during displacement of the condenser lens across the original axis, XY, of the system; the new optical axis is represented by the broken line. Only the limiting rays are illustrated (not to scale). The optical system forms a real image of the source of illumination, this image lying approximately at the iris plane of the eye under examination* section moves in the direction of displacement of the condenser lens ('with' movement—Fig. 2). The middle reflex is ring shaped and arises at the fringe of the macula where the retina reaches a maximum thickness and is convex towards the vitreous cavity.[7] In contrast to the extramacular reflex, however, this macular reflex displays an 'against' movement with respect to the condenser lens. The foveal pit frequently generates a third reflex, this demonstrating a small 'with' movement during shift of the condenser lens. The direction of movement of these reflexes is determined by the concavity or the convexity of the reflecting surface (*vi*).

Alterations of the curvature with pathological retinal elevations cause either a shift of the retinal light reflexes (manifest as a readily evident 'jump' of the reflexes) or a reversal of the direction of movement at the site of the detachment (manifest as a contrasting counter movement of light reflexes with respect to those of the surrounding area). By moving the condenser lens sequentially in two or more meridians, the extent of the abnormal area of elevation can readily be defined.

Discussion

RETINAL SURFACE LIGHT REFLEXES

The glistening light reflexes arise through reflection at the interface between the vitreous, with its lower refractive index, and the internal limiting membrane of the retina.[8] The surface reflexes are best seen at illuminating wavelengths of less than 540 nm (that is, red-free light) and become progressively more difficult to see with monochromatic light of longer wavelengths. Above 600 nm the reflexes are, for practical purposes, invisible.[9] The reflexes are generally of greater intensity in the fundi of young or hypermetropic persons and in darkly pigmented fundi, whereas detachment of the posterior vitreous face generally reduces them.

Previous writers have concentrated on detailed descriptions of the morphology of the surface light reflexes, based often on painstaking and meticulous clinical observations; while frequently describing the reflexes as being 'highly mobile and elusive',[10] possessing 'constant movement,'[10] or (erroneously) as 'shifting irregularly',[11] the observers would appear to have failed to record the value of the motions of these shifting reflexes. Thus, a fine 'granularity' of the extramacular reflex, called Gunn's dots,[12] has been attributed to the processes of Mueller's cells abutting on the internal limiting membrane, and the Weiss light reflex,[13] parallel to the nasal border of the optic disc, has been ascribed to the convexity of the neural fibres as they turn posteriorly to enter the optic disc. In addition the normal fundal light reflexes sometimes show striations along the direction of the retinal nerve fibre layer.

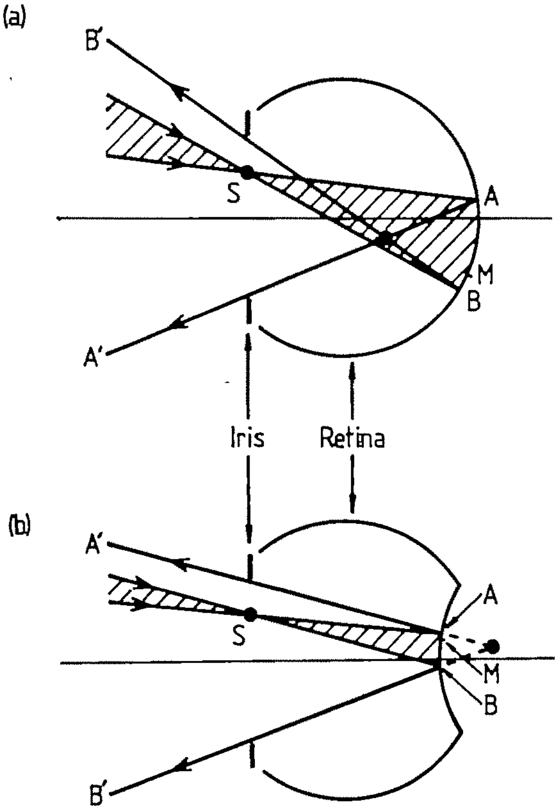

Fig 4 *Formation of the secondary image of the light source image* (S) *by the limiting rays* AA′ *and* BB′ *after specular reflection at the retinal surface of the eye under examination (not to scale). Cross-hatching represents the illuminating pencils of rays. The secondary image, represented by the unmarked dot, forms a real image in areas of concavity* (a) *and a virtual image in areas of convexity* (b) *During indirect ophthalmoscopy the secondary image in both cases will be perceived as an area of maximum retinal light reflex* (M) *on the retinal image* (AMB)

THE OPTICS OF SHIFTING RETINAL LIGHT REFLEXES

The condensing lens during indirect ophthalmoscopy produces an image of the light source positioned approximately at the iris plane of the eye under examination (Fig. 3a). Displacement of the lens across the optical axis of the system is accompanied by a relatively greater lateral displacement of this image in the direction of lens movement (Fig. 3b).

This image of the light source at the pupillary plane of the eye under examination may be regarded as a point source of light illuminating the retina. The

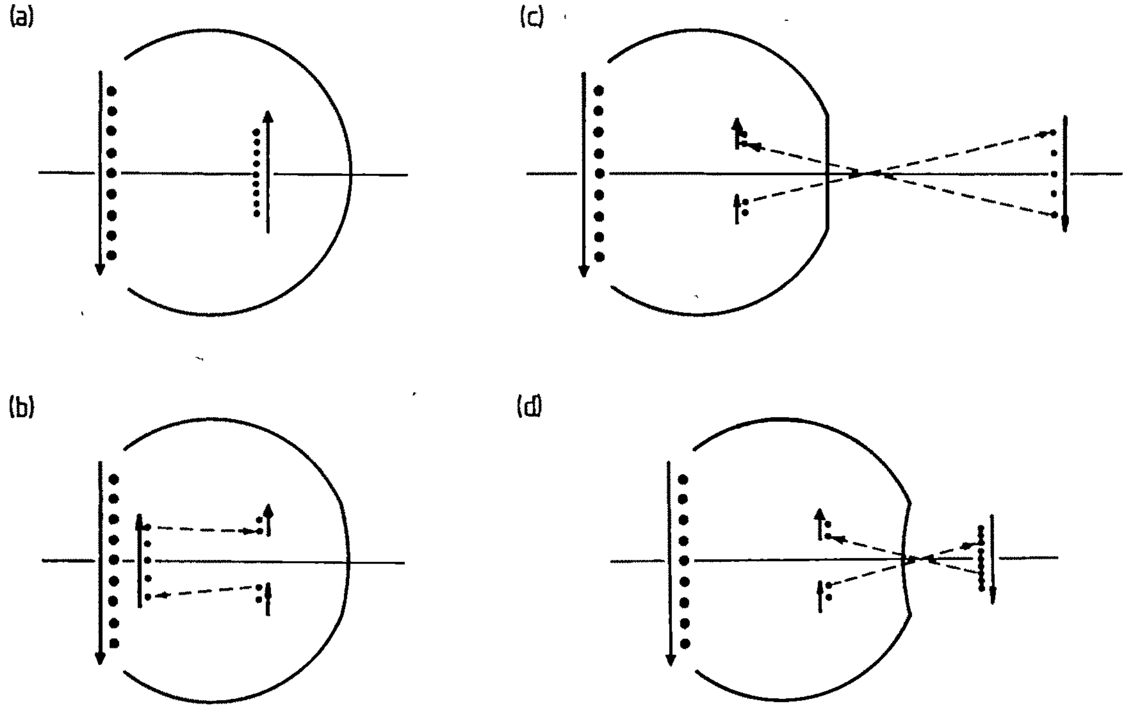

Fig. 5 *The loci of the secondary image (small dots) during movement of the light source image (large dots) across the pupil of the eye undergoing indirect ophthalmoscopy The curved surfaces represent the retina (not to scale) The locus in* (a) *represents that of the major light reflexes from the concave surfaces of the normal eye In* (b), *a shallowing of the concavity is associated with an image 'jump' at the edges of the lesion There is a reversal of image movement once the elevation becomes planar* (c) *or when it is convex* (d). *In addition, there is a transient reduplication of the secondary images in these two phases (see text)*

specular reflections (arising from the mirror-like properties of the retinal surface) will produce a zone of bright reflex on the retina (AMB in Figs. 4a and 4b), this reflex being greatest where the incident ray and its reflected ray coincide (points M in Fig. 4). As illustrated in Fig. 4a, the concave surface produces reflex highlights on the side of the retina *opposite* to that of the displacement of the light source (or lens). In contrast, the convex surface will have highlights on the same half of the retinal surface as that of the lens displacement (Fig. 4b).

As the lens is moved across, so the light source image traverses the pupil and so the highlight moves across the *retina* 'against' the lens movement with a concave surface (Fig. 5a) and 'with' the lens movement for a convex surface (Fig. 5d) After allowance for the inversion of the retinal image (and hence the light reflexes) as formed by the condensing lens, the net result is a 'with' movement of the reflexes (in relation to the condenser lens) for a concave surface and an 'against' movement for a convex surface.

SENSITIVITY OF THE NEW CLINICAL TEST

If an assumption is made of uniform concavity for the retinal surface, it is possible to describe a locus, during the movement of the condenser lens, of the point of maximal light intensity after reflection at the retinal surface. In clinical practice this image of the illumination forms a highlight on the retinal image. The apparent brightness of the light reflex is dependent on the proximity of the image of the light source and the retinal surface.

A uniform concavity would be associated with a linear movement at the image plane (Fig. 5a). Small degrees of retinal elevation, reducing the concavity, cause an image 'jump' at the edges of the lesion (Fig. 5b); this 'jump', to an image plane remote from the retina, is associated with a reduced intensity of the reflexes in the area of elevation. When the concavity is raised to a planar configuration (Fig. 5c), the locus can become more complex, having a mixture of both a 'with' and an 'against' movement. The former image results from the concave portion of retina and the latter from the planar (elevated) portion. The image formed by the planar surface is, because of its relative remoteness from the retina, of lower intensity than that from the concave (normal) retina. Indeed the author considers it probable that this

Table 1 *The central retinal elevation (µm) required to produce a 1°, a 5°, or a 10° 'jump' of the retinal surface light reflex at the edge of various diameters of retinal lesion. The derivation of these values is detailed in the appendix, as are the assumptions made during the calculations*

Diameter of lesion (mm)	*Elevation (µm) to cause an image jump of*		
	1°	*5°*	*10°*
0 5	0·8	1·0	1 1
1 0	2·7	3·9	4·2
1 5	5 0	8·4	9·1
2·0	7 6	14·1	15·8
3 0	13·4	28 8	33 7
4·0	19·6	47 1	57 3

Table 2 *The central retinal elevation (µm) required to cause convexity of various diameters of retinal lesion in an eye of average dimensions*

Diameter of lesion (mm)	*Minimum central elevation for convexity (µm)*
0 5	2 6
1·0	10·4
1 5	23 5
2·0	41·7
3 0	94 1
4·0	167·8

reduced intensity of the light reflexes over areas of shallow retinal elevation contributes to the typical 'lustreless', reflex-free, clinical appearance of macular oedema. Convexity (Fig. 5d) is associated with a marked image 'jump' and also a reversal of image movement.

The new test proves to be extremely sensitive to small elevations of the retina (Appendix). A 1° 'jump' subtended at the observer pupil in the pupillary plane represents approximately 0·37 mm of movement at the retinal plane in an eye of average dimensions. Such an image 'jump', of 1°, occurs with extremely small elevations of the retina—for example, with less than 1 µm at the centre of a lesion 0·5 mm diameter and with 20 µm for a lesion 4 mm across (Table 1). Similarly, elevation to convexity (with concomitant reversal of the light reflex movements) occurs, again, with shallow subretinal fluid—namely, with greater than 2·6 µm central depth for a 0·5 mm lesion and approximately 0·17 mm for a lesion of 4 mm diameter (Table 2)

Appendix

The magnitude of 'jump' as the principal ray crosses the edge of an area of retinal elevation can be calculated The case of the least degree of elevation is considered here, in which the elevation is very shallow and the raised area still concave. In practice, an elevation of such shape is infrequent, but such a calculation provides a useful guide as to the sensitivity of the new clinical test.

During indirect ophthalmoscopy the optics are equivalent to the entrance pupil of the observer lying at the iris plane of the patient In addition the centre of the observer entrance pupil bears a very close and almost constant relationship to the light source image at this plane, even with lateral displacement of the condenser lens Because of this constant relationship between the light source image (S in Fig. 7) and the optics of the observation system, the image 'jump' is defined in this work as the angle subtended at the source image in the iris plane (angle β in Fig 7)

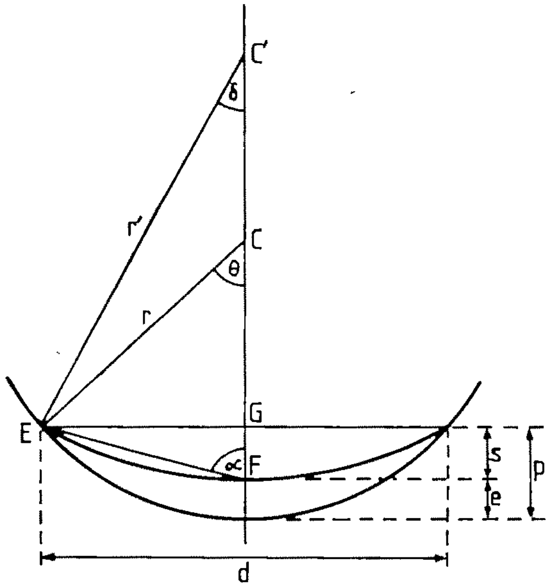

Fig 6 *Geometry associated with a central elevation, e of the retina, from its original radius of curvature, r, to a new concavity with radius r' (and centres of curvature C and C' respectively) The geometry is discussed in the Appendix.*

With reference to Fig 6
In right-angled triangle CEG,

$$r^2 = (d/2)^2 + CG^2$$

$$\text{or, } CG = \sqrt{r^2 - d^2/4}$$

$$\text{But, } p = r - CG$$

$$\text{or, } p = r - \sqrt{r^2 - d^2/4}$$

$$\text{Also, } \theta = \arcsin(d/2r) \qquad \text{Eq 1}$$

In right-angled triangle EFG,

$$\alpha = \arctan(d/2s)$$

$$\text{or, } \alpha = \arctan[d/(2(p-e))] \qquad \text{Eq 2}$$

In isosceles triangle C'EF,

$$\delta = 180 - 2\alpha \qquad \text{Eq 3}$$

In right-angled triangle C'EG,

$$\sin\delta = d/2r'$$

$$\text{or, } r' = d/(2\sin\delta) \qquad \text{Eq 4}$$

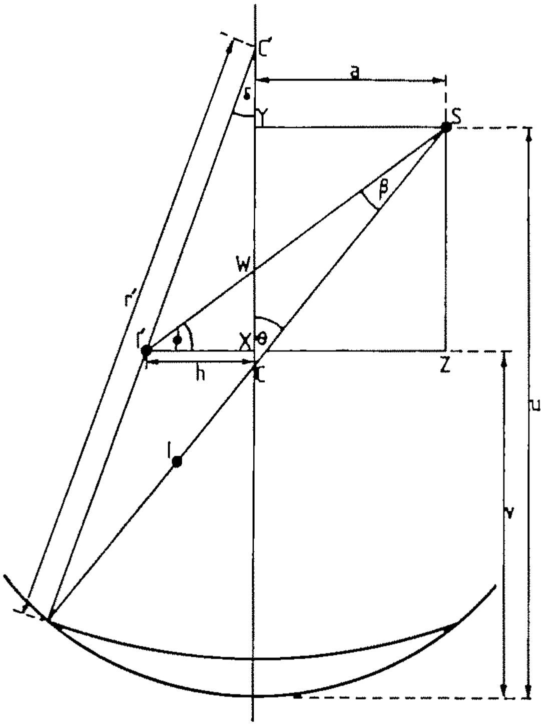

Fig 7 *Geometry associated with the calculation of the angular image 'jump', β, occurring at the edge of an area of concave retinal elevation. Point S represents the light source image at the pupillary plane, I the secondary image formed by specular reflection on the normal concavity of the retina, and I' the secondary image formed by the elevated retina. Further detail is given in the Appendix*

With reference to Fig 7

By the rule of image formation in mirrors,

$$1/(v-e) = 2/r' - 1/(u-e)$$

$$\text{or, } v = [ur' + 2e(u-r'-e)]/[2(u-e)-r'] \qquad \text{Eq 5}$$

where 'e' is the central retinal elevation (Fig 6).

In right-angled triangle C'I'X,

$$\tan\delta = h/(r'+e-v)$$

$$\text{or, } h = (r'+e-v)\tan\delta \qquad \text{Eq 6}$$

In right-angled triangle CSY,

$$\tan\theta = a/(u-r)$$

$$\text{or, } a = (u-r)\tan\theta \,. \qquad \text{Eq.7}$$

In right-angled triangle SI'Z,

$$\tan\phi = (u-v)/(h+a)$$

$$\text{or, } \phi = \arctan[(u-v)/(h+a)] \qquad \text{Eq 8}$$

Finally, in triangle CWS,

$$\angle I'WC = \beta + \theta$$

$$\text{or, } \beta = \angle I'WC - \theta$$

$$\text{But, } \angle I'WC = 90 - \phi \quad (\text{Because } \angle I'WC = \angle I'WX)$$

$$\text{Thus, } \beta = 90 - \phi - \theta \qquad \text{Eq 9}$$

On the assumption that the typical eye has a radius (r) of 12 mm and that the pupillary plane lies approximately 3 mm central to the anterior pole of the eye (making 'u' approximately 21 mm), then the image 'jump', β, can be calculated in terms of two other factors—the diameter of the retinal elevation (d) and the degree of central elevation (e) The angular image 'jump', β, given by equation 9 is derived by sequentially solving equations 1 to 8

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Angiolymphoid hyperplasia with eosinophilia involving the lacrimal gland: case report

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SUMMARY A case is described of a 25-year-old male who developed angiolymphoid hyperplasia with eosinophilia involving the tissue over the left parotid gland and subsequently involving the right lacrimal gland with proptosis. Treatment was by excision.

Angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon lesion which presents as one or more nodules involving the dermis or subcutaneous tissues mainly of the head or neck but occasionally at other sites.[1] It is characterised by lymphoid aggregates with germinal centres, tissue eosinophilia, vascular proliferation with typical plump endothelial cells, and variable fibrosis. In some cases blood eosinophilia is present. We report a case in which the initial presentation was with a swelling over one parotid gland with subsequent involvement of the contralateral lacrimal gland.

Case report

A 25-year-old male of Asian descent, but resident in the UK since birth, presented with a three-month history of a soft diffuse swelling in the region of the left parotid gland. The swelling was painless, and there were no other abnormalities on clinical examination of the head or neck. A parotid sialogram was normal, and a diagnosis of a lipoma overlying the parotid gland was made. The swelling slowly enlarged over the following 10 months, and therefore a superficial parotidectomy was undertaken. By this time the patient had begun to develop slight swelling in the region of the right lacrimal gland. A differential white blood cell count at this time showed 66% neutrophils, 23% lymphocytes, and 11% eosinophils.

Over the next nine months the swelling above the right eye increased and a marked proptosis developed (Fig. 1). There was no ophthalmoplegia, but the patient experienced considerable discomfort. A CT scan demonstrated the lacrimal gland swelling and also swelling of the medial, lateral, and inferior rectus muscles of the right orbit (Fig. 2). Excision of the lacrimal gland was carried out. At operation it

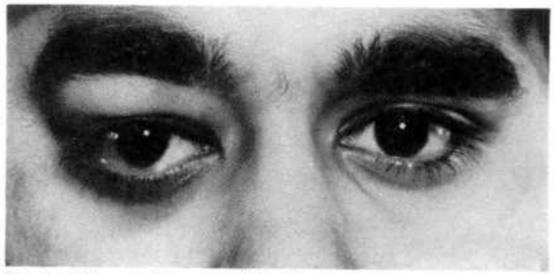

Fig. 1 *There is downward displacement of the globe by swelling in the lacrimal region.*

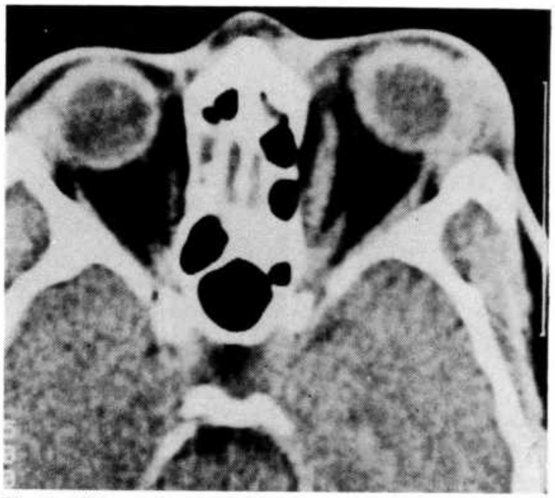

Fig. 2 *CT scan demonstrating mild proptosis and a mass above and lateral to the right globe.*

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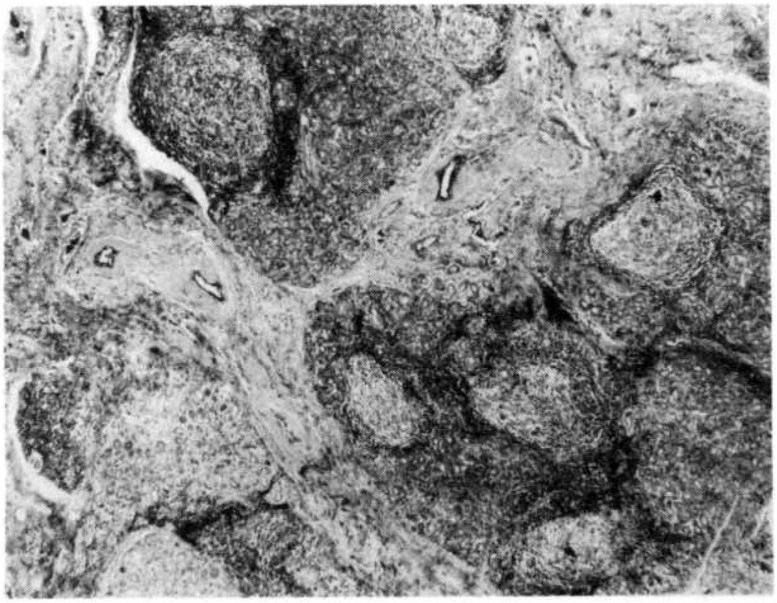

Fig. 3 *Photomicrograph of lacrimal gland showing fibrosis and prominent lymphoid follicles with germinal centre formation. Haematoxylin and eosin, ×45.*

was found to be infiltrated by a mass arising from its anterior part. Some of the apparently normal gland was left in order to facilitate tear production, and the operation was followed by rapid resolution of the proptosis and associated symptoms.

The patient was last seen 10 months after his second operation and had no evidence of any other swellings, either in the head and neck region or elsewhere over the body.

PATHOLOGY

The specimen from the parotid region consisted of part of the parotid gland and superficial fibrous tissue measuring 9·0×4×1·5 cm. The lacrimal gland specimen was two pieces of light brown tissue measuring in total 3·0×2·0×0·6 cm. Histologically the two specimens showed similar features which in the parotid specimen were predominantly in the tissue superficial to the parotid gland, while the deeper part of the gland was unaffected. In the second specimen the changes were seen within the lacrimal gland with extension into the surrounding connective tissue. In both specimens there was marked fibrosis and prominent lymphoid follicles, most of which contained germinal centres (Fig. 3). Within the fibrous stroma were many lymphocytes, eosinophils, and mast cells and con-

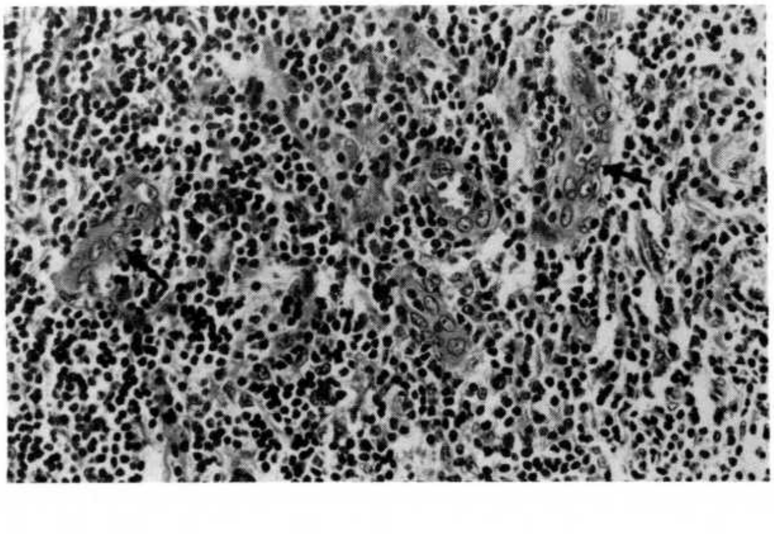

Fig. 4 *Photomicrograph of an area of vascular proliferation within the lacrimal gland. Note the vessels lined by plump endothelial cells (arrows) and the lymphocytic infiltration. Haematoxylin and eosin, ×190.*

siderable capillary proliferation. Many of these proliferating vessels were lined by plump endothelial cells with large vesicular nuclei (Fig. 4). In occasional areas cells of this type were forming small aggregates with no apparent lumen. The appearances in both specimens were those of angiolymphoid hyperplasia with eosinophilia.

Discussion

ALHE was first reported in 1969.[2] It is closely related to Kimura's disease,[3] an entity which has been mainly described in China and Japan, and it has been argued that Kimura's disease is part of the spectrum of ALHE.[1 4 5] Others, however, have emphasised the differences, pointing out that Kimura's disease has different clinical and pathological characteristics.[1] In particular Kimura's disease is said to affect predominantly young males with a high incidence of blood eosinophilia and histologically to show more fibrosis and fewer distinctive endothelial cells. It seems probable that the degree of fibrosis may depend on the duration of the disease before biopsy.

In a report of 116 patients with ALHE submitted to the Armed Forces Institute of Pathology[1] the anatomical sites of the lesions were face and scalp in 100, trunk 4, extremities 12, and miscellaneous 2. In only one case was the diagnosis made preoperatively. Hidayat *et al.*[6] have reported eight cases of ALHE involving the orbit; in none of these cases was the tumour said to involve the lacrimal gland. Eisenberg and Lowlicht[4] have reported a case similar to ours in a 34-year-old female who presented with ALHE involving the right cheek and subsequently developed lacrimal gland involvement.

The consensus is that ALHE is a reactive inflammatory process, and the presence of eosinophils and occasional blood eosinophilia has led to speculation that it represents in an infectious or allergic process or a response to parasitic infection. No parasites or micro-organisms have ever been described within the lesions. Fernandez *et al.*[7] have demonstrated the presence of renin-containing cells in some cases of ALHE and speculate that it may have an angiogenic role. Staining with a polyclonal antibody to human renin was negative in the present case.

ALHE can be successfully treated by local surgery,[8] though complete excision may be difficult.[8] In addition radiation therapy has been effective[9] and intralesional injections of corticosteroids have been successful in some cases.

Professor E Wilson Jones and Dr R W Cox are thanked for advice on the histology of this case

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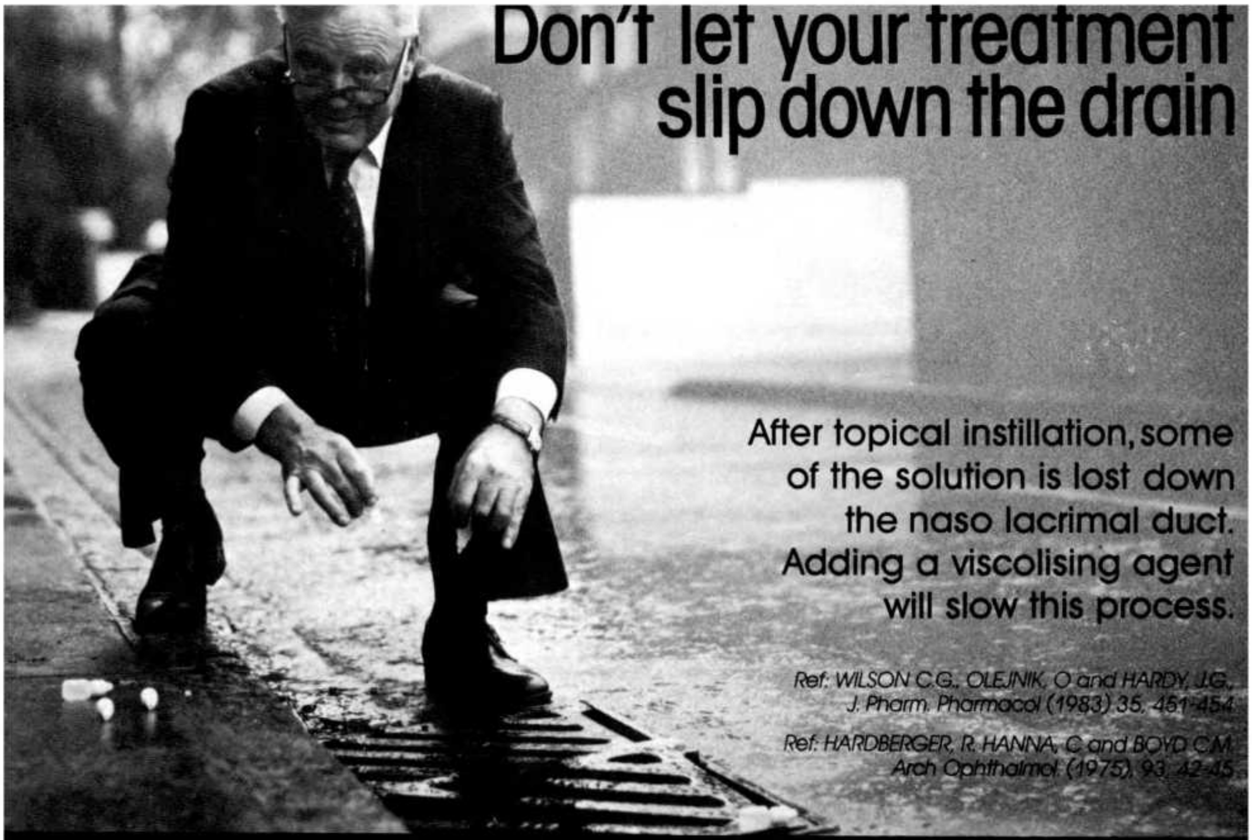

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British Journal of Ophthalmology, 1988, 72, 713–719

Unilateral proptosis as a clinical presentation in primary angiosarcoma of skull

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NITAYA SUWANWELA,[3] AND CHARUS SUWANWELA[2]

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SUMMARY A case is reported of unilateral proptosis of the left eyeball as a unique clinical presentation of primary angiosarcoma of the skull involving the sphenoid and frontal bones and roof of the orbit on the left side of a 32-year-old man. The intraosseous, extradural non-encapsulated, and friable tumour contained cytoplasmic factor VIII-related antigen. After complete removal of the tumour the patient has been well for 10 months of the follow-up period. This case brings the total number of reported primary angiosarcomas of the cranium to nine. All patients were male and most of them were young. The average age was 24 years. The frontal bone seems to be the site of predilection for cranial angiosarcomas. Surgical extirpation, radiation, or combined surgical removal and radiation have been used for treating angiosarcoma of the skull with variable results. It is suggested that angiosarcoma of the skull has a worse prognosis than angiosarcoma of bones other than the cranium because the patient may die of secondary neoplastic involvement of the brain.

Primary new growths of the cranial bones constitute only 2·6% of 500 primary bone tumours in one series[1] and 2·4% of 1610 primary bone neoplasms in another collection.[2] Angiosarcomas are extremely rare among primary malignant tumours of the skull; only eight acceptable cases have appeared in the literature.[3-9] In this communication we report an intraosseous angiosarcoma involving the sphenoid and frontal bones as well as the roof of the orbit and causing unilateral exophthalmos. The latter becomes a unique clinical presentation for angiosarcoma arising in the cranium.

Case report

A 32-year-old man was admitted to hospital because of progressive left proptosis without other associated symptoms or signs for one year.

EXAMINATION

With a slit-lamp the left eye was 15 mm compared with 12 mm for the right eye by measuring from the orbital rim to the most anterior aspect of the cornea. Ocular movements were normal bilaterally Each pupil, 2 mm in diameter, was reactive to light. Visual acuity, visual field, eye ground, and the rest of the physical examination were unremarkable.

A plain x-ray of the skull showed destruction of the lesser wing of the sphenoid bone and posterior wall of the orbit on the left side. Computed tomographic (CT) scans of the cranium gave the following findings on the left side: proptosis, and destruction and expansion of the sphenoid and frontal bones in relation to an enhanced lesion which appeared to extend into the orbit (Figs. 1A, B).

OPERATION

A left frontotemporal craniotomy disclosed an intraosseous, extradural, non-encapsulated, highly vascular, and friable tumour involving the lesser and greater wings of the sphenoid bone, frontal bone, and roof of the orbit. It was firmly adherent to the adjacent dura mater. A small part of the lesion was also adherent to the superior aspect of the bulbar fascia of the left eyeball. The entire neoplasm was removed along with the affected parts of bones,

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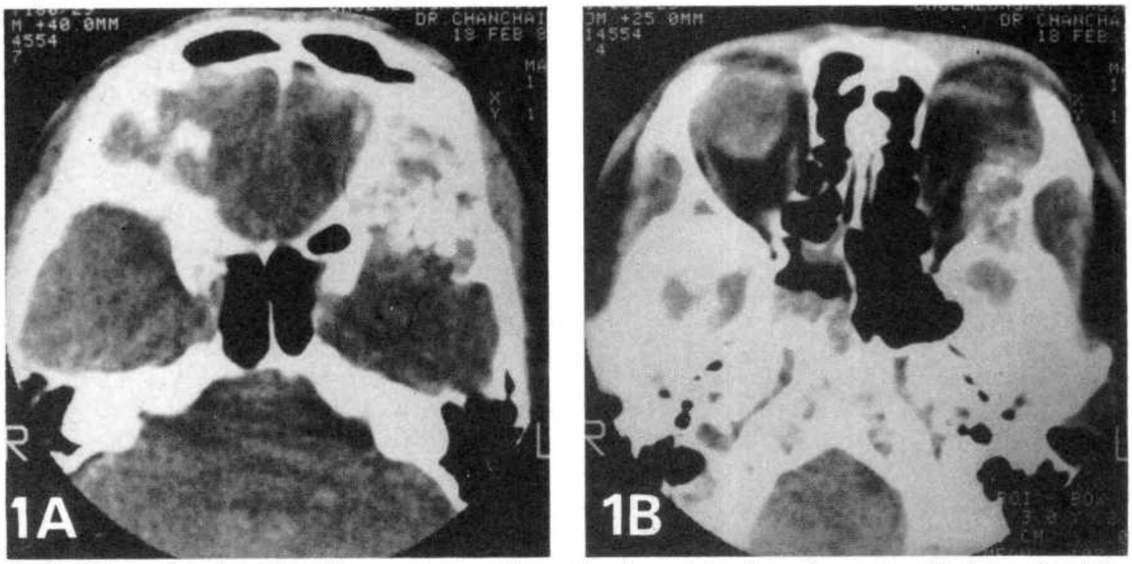


Fig. 1 *CT scan of skull.* A: *Plain CT scan at the base of the cranium shows destruction and expansion of the lesser wing of the sphenoid and frontal bones on the left side with involvement of the diploic space.* B: *The enhanced mass extends into the posterolateral part of the left orbit.*

bulbar fascia, and dura mater. The dural defect was grafted with temporal fascia. There was profuse bleeding, which required 10 units of blood for transfusion. The adjacent part of the brain was free from tumour infiltration. The patient recovered uneventfully.

PATHOLOGICAL EXAMINATION

Multiple pieces of haemorrhagic tissue with fragments of bones, about 2·5 ml in combined volume, were fixed in 10% formalin. The largest fragment of tumour, 2·5 cm in greatest dimension, was attached partly to dura mater; it had a spongy cut surface. These tissue fragments were embedded in paraffin and stained with haematoxylin and eosin (H-E). Gomori's silver impregnation for reticulin fibres was also done. Moreover, the peroxidase-antiperoxidase (PAP) indirect immunohistochemical method was used on paraffin-embedded tissue sections for localisation of factor VIII-related antigen, a protein synthesised primarily by endothelium,[10-12] in the tumour cells. A fragment of the spleen was similarly processed as a control.

Microscopically the lesion was a highly vascular neoplasm invading bone and dura mater (Fig. 2). Neoplastic blood vessels were lined by plump cuboid-to-ovoid endothelial cells having pleomorphic and hyperchromatic nuclei. Scattered individual vessels, anastomosing vascular channels, and papillary formations were noted (Fig. 3). Nevertheless large blood-filled spaces lined by endothelial cells that were not strikingly atypical were also observed. The stroma between recognisable blood vessels was composed of loose myxomatous tissue that contained stellate cells as well as elongate or spindle-shaped cells (Fig. 4A) and neoplastic cells similar to those lined the vascular channels. These extravascular tumour cells tended to be in clusters or disseminated individually (Fig. 4B). Gomori's silver impregnation disclosed that the tumour cells were within the reticulin sheath of the vessels in the area where vascular spaces were present (Fig. 4C). Reticulin fibres also surrounded clusters of the neoplastic cells in the zone where the tumour cells were grouped within the myxomatous matrix (Fig. 4D). Encircling of the argyrophilic fibres round the individual tumour cells was not seen. Factor VIII-associated antigen was often present in the cytoplasm of the tumour cells that lined the vascular lumina and in the myxomatous stroma (Fig. 5). Hence the endothelial nature of the tumour cells was confirmed immunohistochemically.

The pathological diagnosis was an angiosarcoma involving the sphenoid and frontal bones and roof of the orbit on the left side and invading the adjacent dura mater and superior aspect of the bulbar fascia of the left eyeball.

POSTOPERATIVE COURSE

The patient was discharged 17 days after admission to hospital. CT scans of the skull one month and nine months after surgical intervention revealed no evidence of tumour. There was a decrease in the size

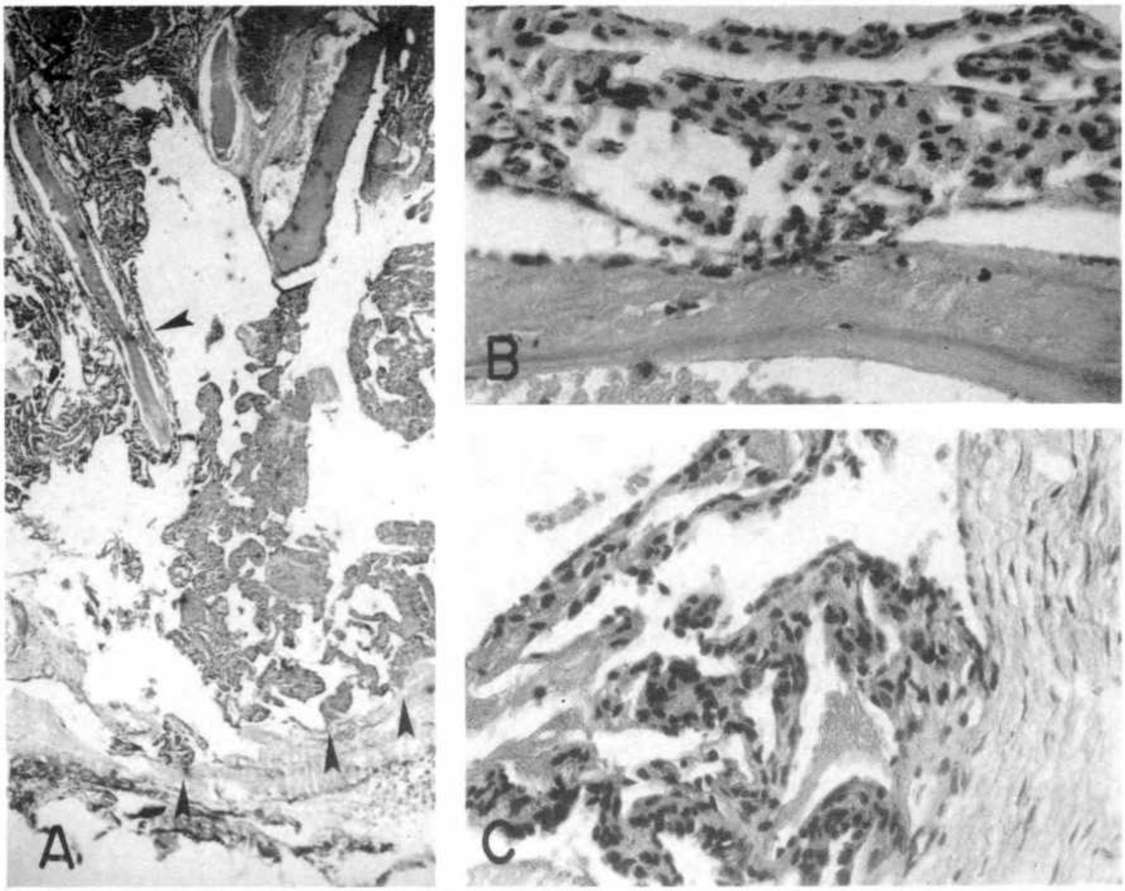


Fig. 2 *Invasion of angiosarcoma into bone and dura mater.* A: *The angiosarcoma invades bone trabecula (upper arrowhead) and dura mater (lower arrowheads) (H-E, ×44).* B: *The area indicated by the upper arrowhead in A demonstrates focal invasion of the tumour cells into the edge of the bone trabecula (H-E, ×348).* C: *The region indicated by the left lower arrowhead in A exhibits infiltration of the neoplastic cells into the dura mater (H-E, ×348).*

of the shadow of soft tissues at the operative site. The left exophthalmos was improved. The patient could perform his daily work as usual.

Discussion

GENERAL CONSIDERATIONS

The term 'angiosarcoma' as used here is regarded as synonymous with the following terms found in the literature: angioendothelioma, malignant angioma, angiofibrosarcoma, haemangioblastoma, angioblastic sarcoma, malignant haemangioendothelioma, haemangioendothelioblastoma, malignant angioblastoma, haemangioendotheliosarcoma, intravascular endothelioma, malignant endothelioma, and malignant bone aneurysm.[13,14]

Anastomosing vascular channels lined by pleomorphic endothelial cells which often form papillae are diagnostic of angiosarcoma.[8,14] These histopathological features were also seen in our patient's tumour. Moreover, the endothelial nature of the tumour cells is further confirmed by localisation of cytoplasmic factor VIII-related antigen. Hence the pathological diagnosis of the angiosarcoma is considered as unequivocal in our case.

The main intraosseous position with minimal infiltration of the bulbar fascia, as noted surgically, makes us conclude that the current angiosarcoma is primarily intraosseous, with secondary invasion into the superior aspect of the bulbar fascia. It is hard to imagine reciprocally that a small primary angiosarcoma of the latter will extend widely to become an intraosseous lesion within the sphenoid and frontal bones as well as the orbital roof. A lesion of bones forming the orbit may cause proptosis.

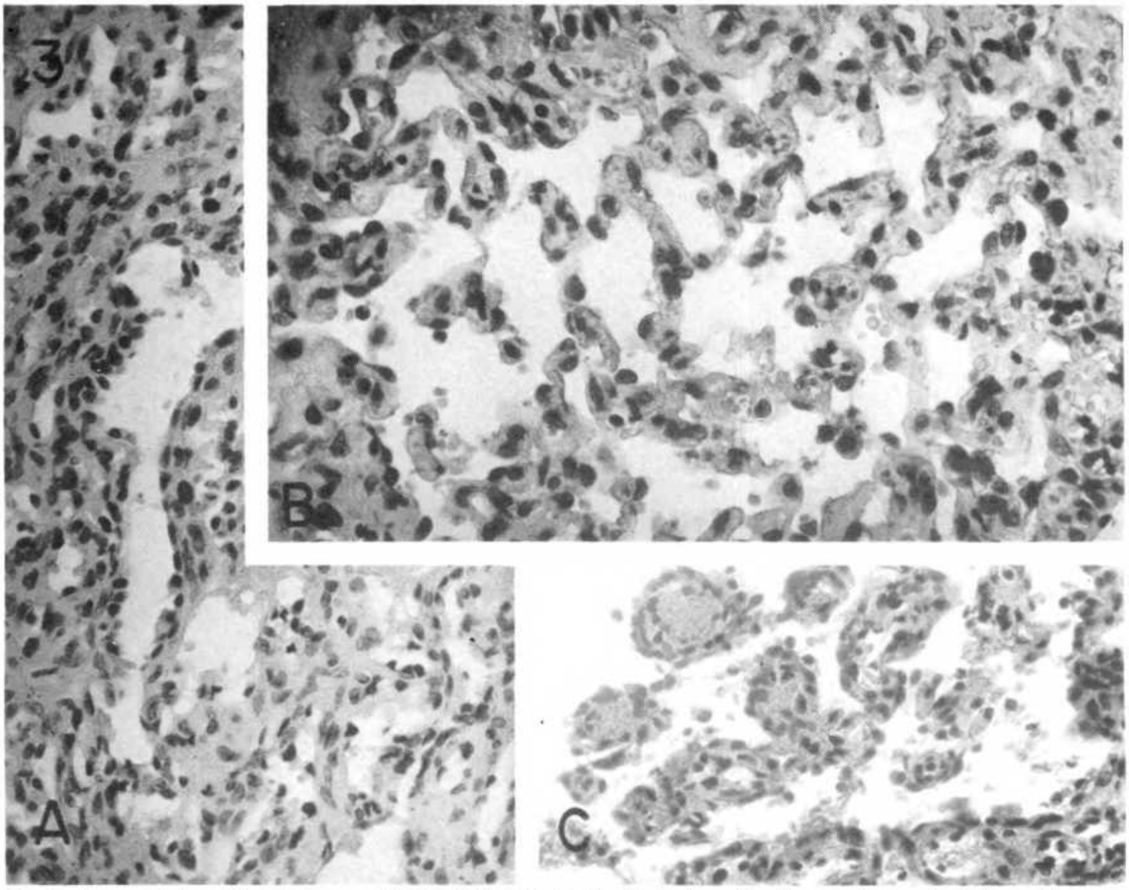


Fig. 3 *Histopathology of angiosarcoma (H-E, ×337 each).* A: *Blood vessels are lined by neoplastic endothelium with pleomorphic and hyperchromatic nuclei.* B: *Anastomosing cords of pleomorphic endothelial cells are shown.* C: *Papillary formations of endothelial tumour cells are shown.*

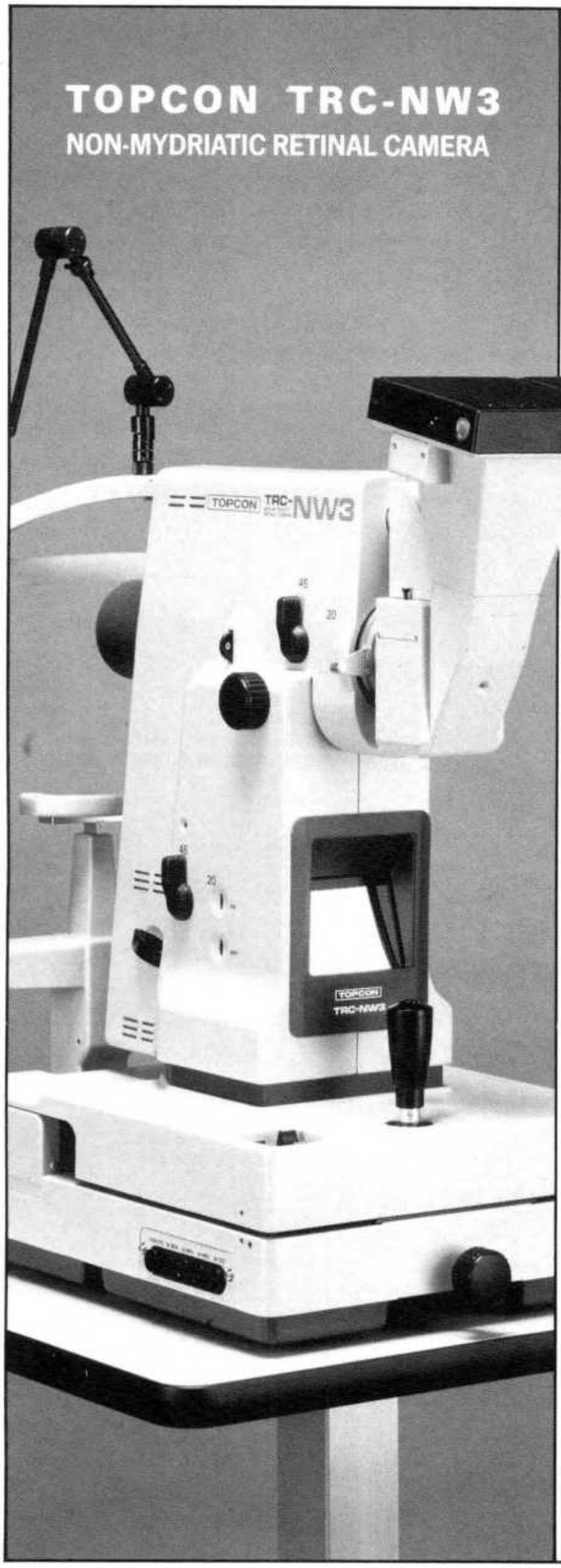
DIFFERENTIAL DIAGNOSIS

The present angiosarcoma of bones must be distinguished from such lesions as meningioma, haemangiopericytoma, and primary intravascular papillary endothelial hyperplasia. Attachment to the dura mater, bony invasion, and papillary formations suggest that the tumour is a meningioma, especially the papillary type. However, the absence of the tumour capsule, meningocytes, cellular whorls, and intranuclear vacuoles, and the presence of cytoplasmic factor VIII-related antigen in the tumour cells exclude a meningioma.[15, 16] We also do not consider our patient's tumour to be a haemangiopericytoma of the meninges[17] or of the orbit.[18] The absence of reticulin fibres round individual tumour cells is not a feature of haemangiopericytoma. Moreover, the neoplastic cells were mainly intravascular rather than perivascular. Hence they were not pericytes. According to Nadji *et al.*[11] tests for factor VIII-associated antigen are persistently negative in cells of haemangiopericytoma.

Primary intravascular papillary endothelial hyperplasia may mimic an angiosarcoma.[19–21] However, the endothelium in this condition is benign, as the name 'hyperplasia' implies. Although the overgrown endothelium in this condition may form intravascular papillae, it lacks nuclear pleomorphism. By contrast, the current lesion had endothelium that showed pleomorphic nuclei and invaded the surrounding tissues. Hence the lesion should be named as angiosarcoma rather than as primary intravascular papillary endothelial hyperplasia.

BRIEF REVIEW OF LITERATURE

To our knowledge 12 angiosarcomas of the skull have been reported.[3–9, 14, 22–24] However, four of them are



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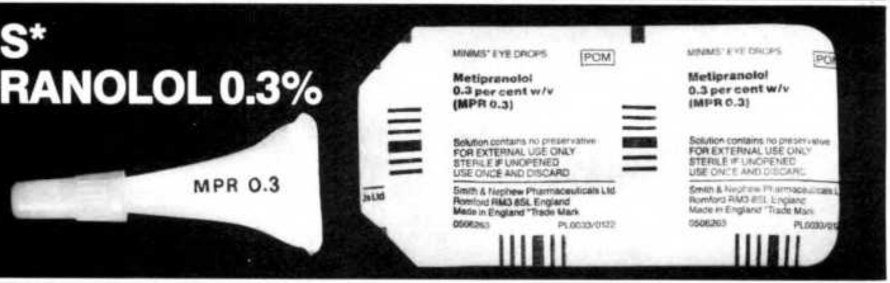

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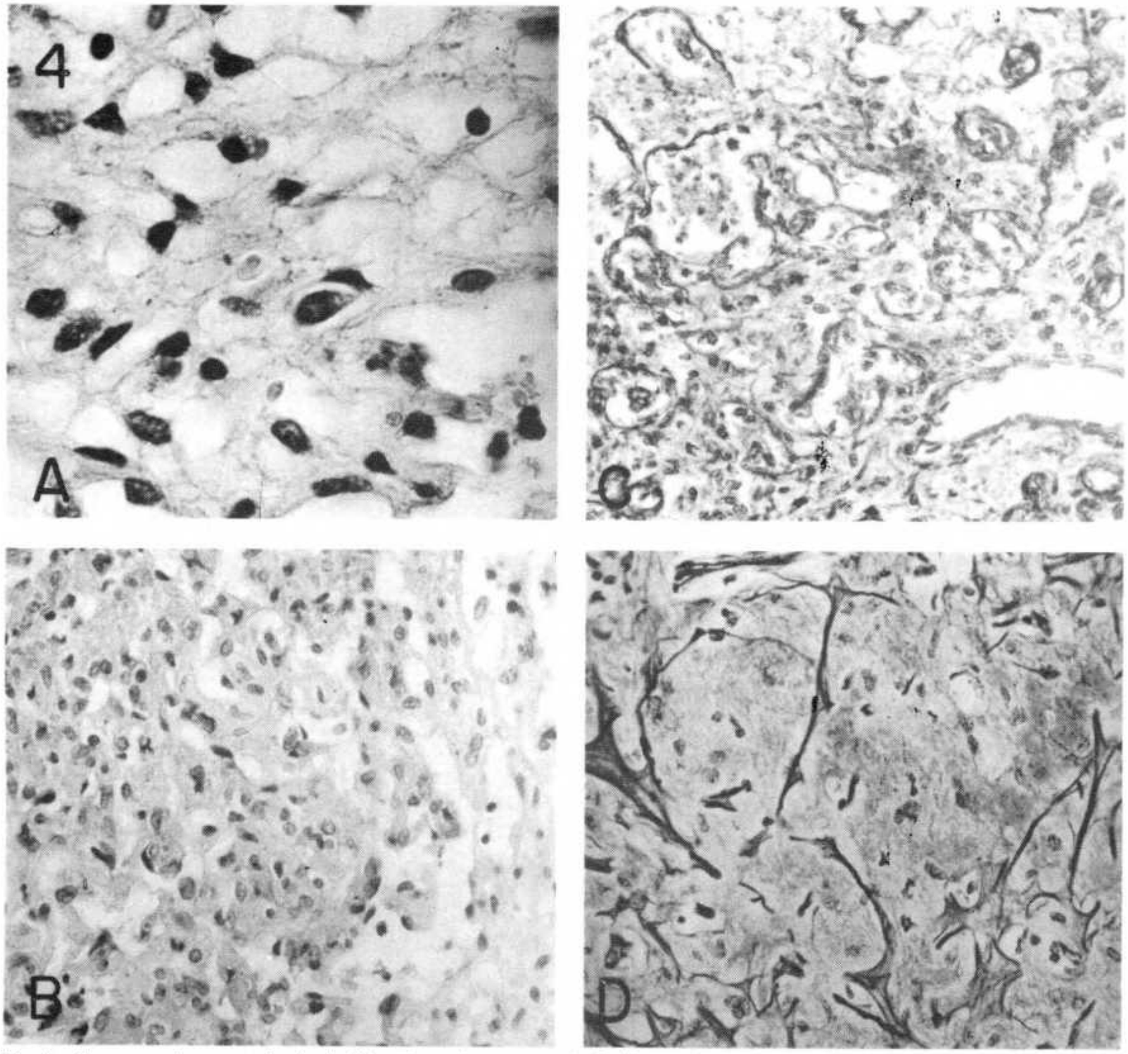

Fig. 4 *Stroma and pattern of reticulin fibres in angiosarcoma.* A: *Stellate and spindle-shaped cells lie within the loose myxomatous matrix of the tumour (H-E, ×886).* B: *The tumour cells are clustered in the loose myxomatous stroma (H-E, ×354).* C: *Reticulin fibres surround blood vessels that are lined by neoplastic endothelium. Some blood vessels are partly filled by endothelial cells (Gomori's silver impregnation, ×354).* D: *Clusters of the tumour cells in the myxomatous matrix are surrounded by a few argyrophilic fibres (Gomori's silver impregnation, ×354).*

excluded herewith because of inadequate pathological confirmation of the lesions.[14 22–24] Thus nine angiosarcomas of the cranium including our case are considered in this discussion.[3–9] The youngest patient was 3 months old[4] and the oldest was 50 years.[8] Most patients were young. Three were children less than 8 years old.[1 2 8] The average age was 24 years. All persons were male. A local mass or swelling was the usual clinical presentation. Only our patient presented with unilateral proptosis.

The tumour involved the frontal bone in four cases,[5 7–9] parietal bone in two cases,[6] temporal bone in one case,[3] sphenoid and frontal bones as well as the orbital roof in one case (current patient), and maxilla in one case.[4] Thus the frontal bone seems to be the favoured site for angiosarcomas of the skull.

Resection, radiation, or combined resection and radiation were frequently used in treating the angiosarcomas of the cranium, with variable results. Surgical treatment seems to give encouraging results in some patients, in that they have been alive for 27 months[4] and 3½ years,[8] but one patient died post-

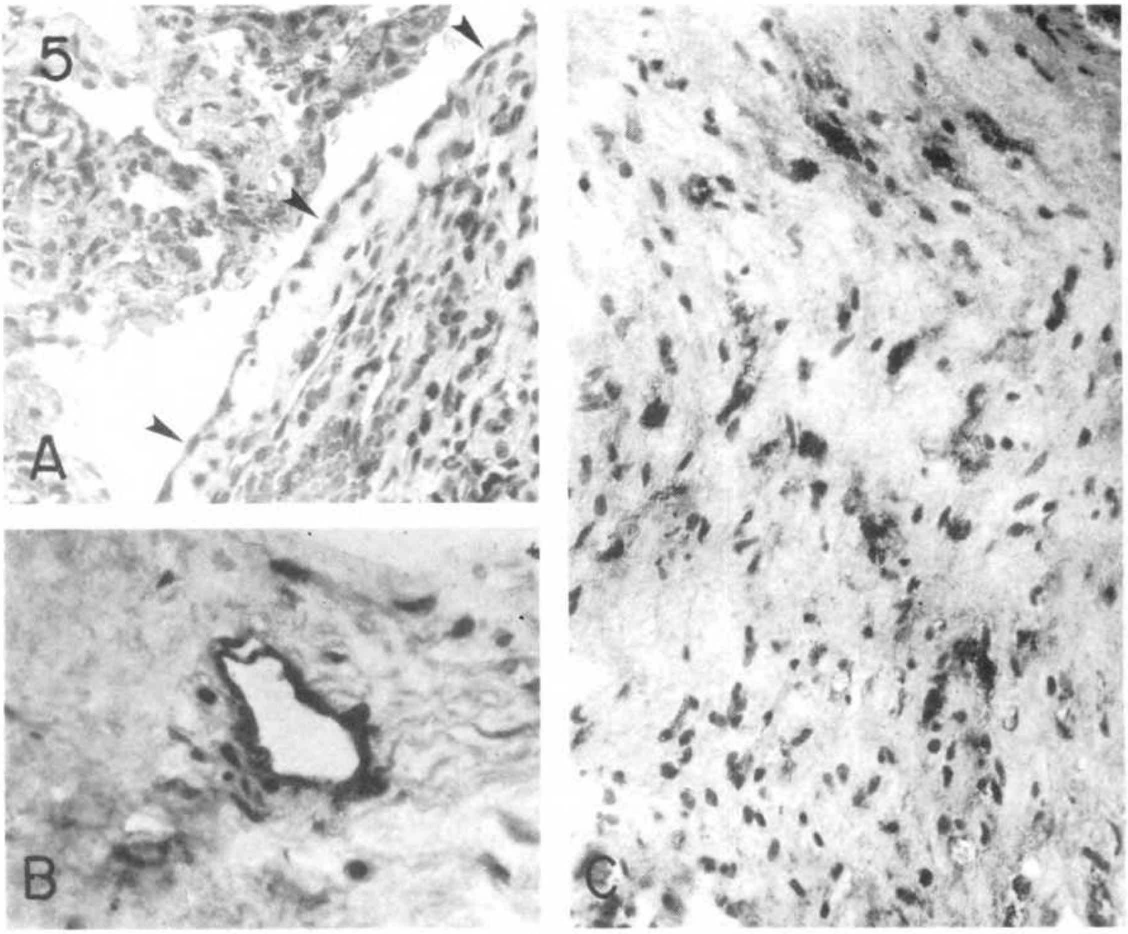

Fig. 5 *PAP indirect immunohistochemical localisation of factor VIII-related antigen in angiosarcoma (×354 each).* A: *The arrowheads point toward a row of endothelial cells that show weak positivity for factor VIII-related antigen in the perikaryon.* B: *A neoplastic blood vessel with endothelial cytoplasm of strong positivity for factor VIII-associated antigen lies within the loose myxomatous matrix.* C: *Neoplastic endothelial cells with strong positivity for cytoplasmic factor VIII-related antigen are disseminated randomly in the loose myxomatous interstitium.*

operatively.[8] A boy who received high doses of radiation for primary and recurrent angiosarcomas of the frontal bones has been well for 12 years,[9] but another boy lived only 9·5 months with radiotherapy.[3] Chow *et al.*[7] believed that a 21-year-old man who had had an angiosarcoma of the frontal bone was cured by combined radiation and resection. The patient first had a biopsy and a course of radiotherapy totalling 6000 cGy over a six-week period. Seven months later he underwent resection, when the tumour site including the surrounding bone and dura mater was removed en bloc. Pathologically, only fibrosis and suture granuloma were seen.[7] Nevertheless we believe that angiosarcoma of the skull may have a worse prognosis than angisarcoma of bones other than the cranium, because the tumour may secondarily involve the brain and the patient dies with increased intracranial pressure, as did the boy reported on by Kinkade.[3]

Professor Samruay Shuangshoti is in receipt of a grant from the Medical Section, Anandhamahidol Foundation, 1985–8, Bangkok, Thailand.

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Book reviews

New Microsurgical Concepts: Posterior and Anterior Segments. Eds. J DRAEGER AND R WINTER Pp. 206. DM 216·00. Karger: Basel. 1987.

It is now 22 years since the International Ophthalmic Microsurgery Study Group (IOMSG) met for the first time as a satellite meeting of the International Ophthalmological Congress of 1966 The importance and success of that first meeting was, as Roper-Hall describes in his opening introductory paper of this book, 'catalytic in establishing ophthalmic microsurgery'. Meetings of the IOMSG have been held every two years, and the transactions of the group have been published by Karger in their continuing series *Advances in Ophthalmology* and now *Developments in Ophthalmology*. This book is a record of the proceedings of the twentieth anniversary meeting of the IOMSG

A wide range of topics are covered, loosely grouped into posterior segment, lasers, cornea, and cataract and glaucoma microsurgery. There are two invited review papers, one on clinically applied silicones and the other on the uses of lasers for microsurgery, which are interesting reviews of the subjects Whereas these two invited articles are reproduced in full, the remaining scientific papers which make up the bulk of this book have apparently been severely edited It seems that every author has been limited to only a few pages, and this condensation has taken place at the expense of data and statements of scientific method, the authors' conclusions appear therefore to be unsubstantiated by facts. Furthermore, these papers have apparently neither been refereed nor read or checked by a native English speaker. No doubt many of the papers were presented to this lively meeting of distinguished ophthalmologists with the aim of provoking argument and discussion, but the reader is left without the privilege of hearing their critical response. These many shortcomings and the high price of 216 DM (approximately £70 sterling) make it hard to recommend this slim volume.

BRUCE NOBLE

Complications in Modern Ophthalmic Surgery. Edited by I STREMPEL Pp. 156. £58·20. Karger: Basel. 1987

This is a festschrift in honour of Professor Wolfgang Straub, and is based on the proceedings of a symposium which was convened in his honour in Marburg on 18 January 1986 The 19 contributions cover most aspects of ophthalmic surgery including lid, anterior segment, vitreoretinal, and strabismus procedures The standard and the scientific contents of individual contributions vary widely, ranging from a simple review of the literature such as in the chapter on complications of posterior chamber implantation to the presentation of detailed results of research studies The latter include reports on tissue changes induced by intraocular lenses, and keratopathy following pars plana vitrectomy with silicone oil Finally there are chapters which concern themselves with new surgical techniques, omitting the topic of complications altogether.

Given the variety of the topics it is difficult to know who this publication is aimed at, though undoubtedly most readers will find something of interest in it

Z J GREGOR

Stereoscopic Atlas of Macular Diseases: Diagnosis and Treatment. Vols. 1 and 2 3rd Edn. By J DONALD M GASS. Pp. 801. £160·00. Blackwell: Oxford 1987.

The third edition of this popular textbook, written by the world authority on the subject, reflects the author's astute powers of observation and his vast experience in the management of macular disease There are two volumes presented in a box and each has a comprehensive and reliable index In place of the 'suggested readings', which appeared at the end of each chapter in the previous editions there is a reference system which substantially increases the value of the book A new chapter on interpretation of fluorescein angiography is clearly presented after the chapter on the normal macula, providing an excellent introduction The colour stereo-wheels are maintained and extended, though the reader must find his own viewer In addition some prints of stereo-angiograms are included, perhaps these are too small to be fully appreciated.

An important feature of this atlas is the striking amount of text, particularly detailed clinicopathological analysis, such as is applied to choroidal neovascularisation The author's eye for detail is reflected in subdivision of certain disorders, such as parafoveal telangiectasis Only rarely, as with discussion of uveal effusion syndrome, does repetition occur or the anecdotal nature of some of the text detract from the facts Chapter 7, on inflammatory diseases of the retina and choroid, covers a wide range from sarcoidosis to rarities such as gnathostomiasis. AIDS and opportunistic infections are included, and an update is given on treatment The chapter on pigment epithelial and retinal toxicity is succinct and refers to the recent finding of desferrioxamine maculopathy The final chapter on laser photocoagulation is thoroughly practical and covers some controversial issues, such as the treatment of pigment epithelial detachments.

This is an excellent book which presents significant new information as part of a comprehensive account of macular disease. Although the price is for specialists, it is not excessive by modern standards. The text should ideally be easily accessible to all ophthalmologists, preferably securely chained to a wall.

CAROL LANE

Note

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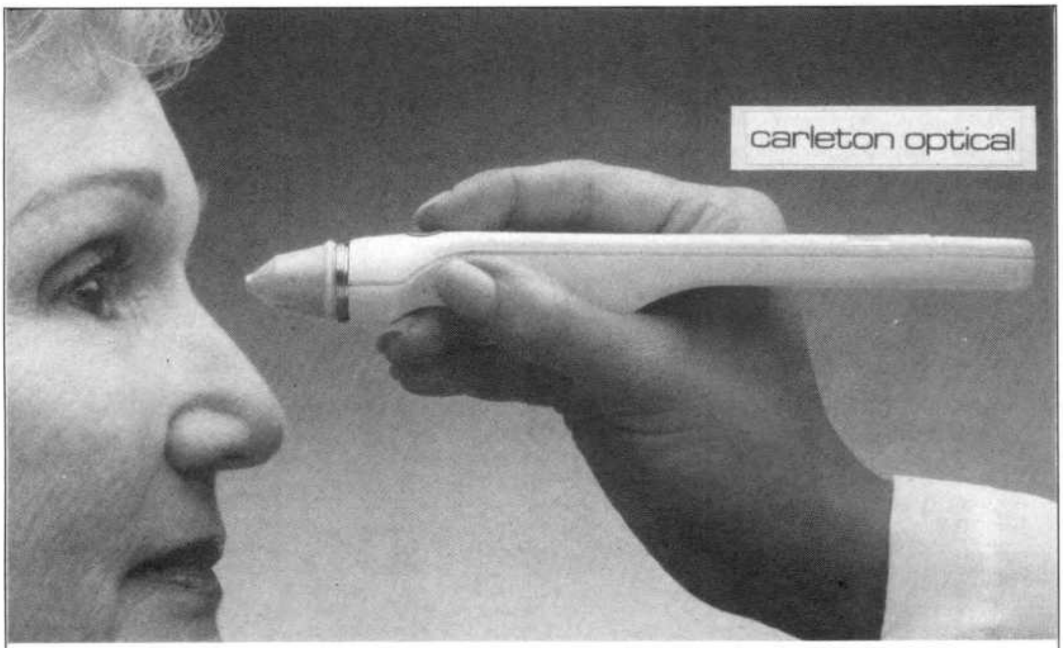

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TABLE OF CONTENTS

ORIGINAL ARTICLES

Traumatic hyphema in a defined population *Robert H Kennedy and Richard F Brubaker*

Optic disk neovascularization and retinal vessel diameter in diabetic retinopathy *Charles A Wilson, Einar Stefánsson, Lee Klombers, Larry D Hubbard, Steven C. Kaufman, and Frederick L. Ferris III*

Cryopexy of the vitreous base in the management of peripheral uveitis *Robert G Devenyi, William F. Mieler, Fred H Lambrou, Brian R Will, and Thomas M Aaberg*

Abnormal scleral findings in uveal effusion syndrome *Robert C Ward, Evangelos S. Gragoudas, David M. Pon, and Daniel M Albert*

Repeated fluid-gas exchange for hypotony after vitreoretinal surgery for proliferative vitreoretinopathy *Jay B Stallman and Sanford M Meyers*

Pseudoinflammatory macular dystrophy *R F Dreyer and Ahmed A Hidayat*

Long-term betaxolol therapy in glaucoma patients with pulmonary disease *Robert N. Weinreb, E Michael van Buskirk, Reuben Cherniack, and Margaret M Drake*

Comparative efficacy of the β-blockers for the prevention of increased intraocular pressure after cataract extraction *David R West, Timothy D Lischwe, Vance M Thompson, and Carl H Ide*

Oculab Tono-Pen, Goldmann applanation tonometry, and pneumatic tonometry for intraocular pressure assessment in gas-filled eyes *Michael W Hines, Bradley F Jost, and Karen L Fogelman*

The value of indices in the central and peripheral visual fields for the detection of glaucoma *C Seamone, R Le Blanc, M Rubillowicz, C Mann, and A Orr*

Analysis of tear proteins in Graves' ophthalmopathy by high performance liquid chromatography *H. A Khalil, R J W de Keizer, and A. Kijlstra*

Optic atrophy in children *Michael X Repka and Neil R. Miller*

Echographic characteristics of benign orbital schwannomas (neurilemomas) *Barry M. Byrne, W A J van Heuven, and Andrew W Lawton*

Progression of visual defects in ischemic optic neuropathy *Lanning B. Kline*

Nasolacrimal drainage system obstruction after orbital decompression *Stuart R Seiff and Norman Shorr*

Corneal edema related to accidental Hibiclens exposure *Richard B. Phinney, Bartley J Mondino, John D. Hofbauer, David M Meisler, Roger H. S. Langston, S Lance Forstot, and Susan C Benes*

Suramin keratopathy *Edward J. Holland, Cy A. Stein, Alan G Palestine, Renato LaRocca, Chi-Chao Chan, Toichiro Kuwabara, Charles E Myers, Rose Thomas, Nanette McAtee, and Robert N Nussenblatt*

Corneal metastatic calcification in Werner's syndrome *I Kremer, A Ingber, and I Ben-Sira*

EDITORIAL

The potential use of quinolones in future ocular antimicrobial therapy *Leonard R Bormann and Irving H. Leopold*

LETTERS TO THE JOURNAL **CORRESPONDENCE** **BOOK REVIEWS**

ABSTRACTS **NEWS ITEMS**

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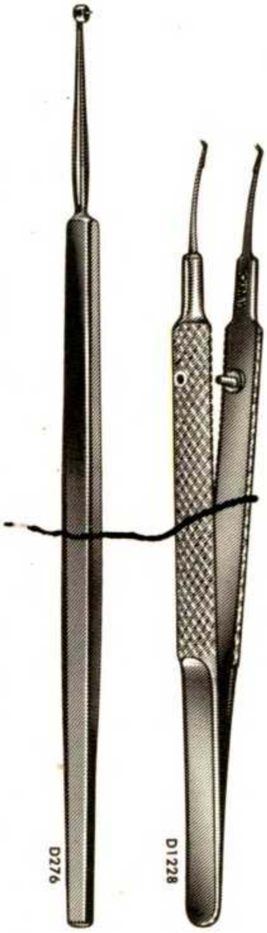

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Contents

Photostress recovery in chronic open angle glaucoma MARK D SHERMAN AND PAUL HENKIND *page* 641

Birdshot chorioretinopathy: clinical characteristics and evolution HILDE A PRIEM AND JENDO A OOSTERHUIS *page* 646

Reflow of obstructed capillaries in the maculae of humans with diabetic retinopathy, observed by fluorescein angiography YASUO YAMANA, YOSHISUKE OKA, YOSHITAKA OHNISHI, TATSURO ISHIBASHI, AND TOYOSHI INOGUCHI *page* 660

Effects of intensified insulin treatment on retinal vessels in diabetic patients O BRINCHMANN-HANSEN, K DAHL-JØRGENSEN, K F HANSSEN, AND L SANDVIK *page* 666

Graves' ophthalmopathy: I. Simple CT estimates of extraocular muscle volume E SVERKER HALLIN AND STEVEN E FELDON *page* 674

Graves' ophthalmopathy: II. Correlation of clinical signs with measures derived from computed tomography E SVERKER HALLIN AND STEVEN E FELDON *page* 678

Graves' ophthalmopathy: III. Effect of transantral orbital decompression on optic neuropathy E SVERKER HALLIN, STEVEN E FELDON, AND JEFFREY LUTTRELL *page* 683

Pharmacokinetics of a 5-fluorouracil liposomal delivery system STEPHEN T SIMMONS, MARK B SHERWOOD, DAN A NICHOLS, ROBERT B PENNE, THEODORE SERY, AND GEORGE L SPAETH *page* 688

Vitrectomy for idiopathic epiretinal membranes causing macular pucker SERGE DE BUSTROS, JOHN T THOMPSON, RONALD G MICHELS, THOMAS A RICE, AND BERT M GLASER *page* 692

Corneal shape and astigmatism: with a note on myopia R A WEALE *page* 696

Addition of hyaluronidase to lignocaine with adrenaline for retrobulbar anaesthesia in the surgery of senile cataract IAN THOMSON *page* 700

Clinical assessment of retinal elevations: a review of methods and a novel clinical technique GEOFFREY E ROSE *page* 703

Angiolymphoid hyperplasia with eosinophilia involving the lacrimal gland H T COOK AND N D STAFFORD *page* 710

Unilateral proptosis as a clinical presentation in primary angiosarcoma of skull SAMRUAY SHUANGSHOTI, PRACHA CHAYAPUM, NITAYA SUWANWELA, AND CHARUS SUWANWELA *page* 713

Correspondence *page* 720

Book review *page* 720

Notes *page* 720

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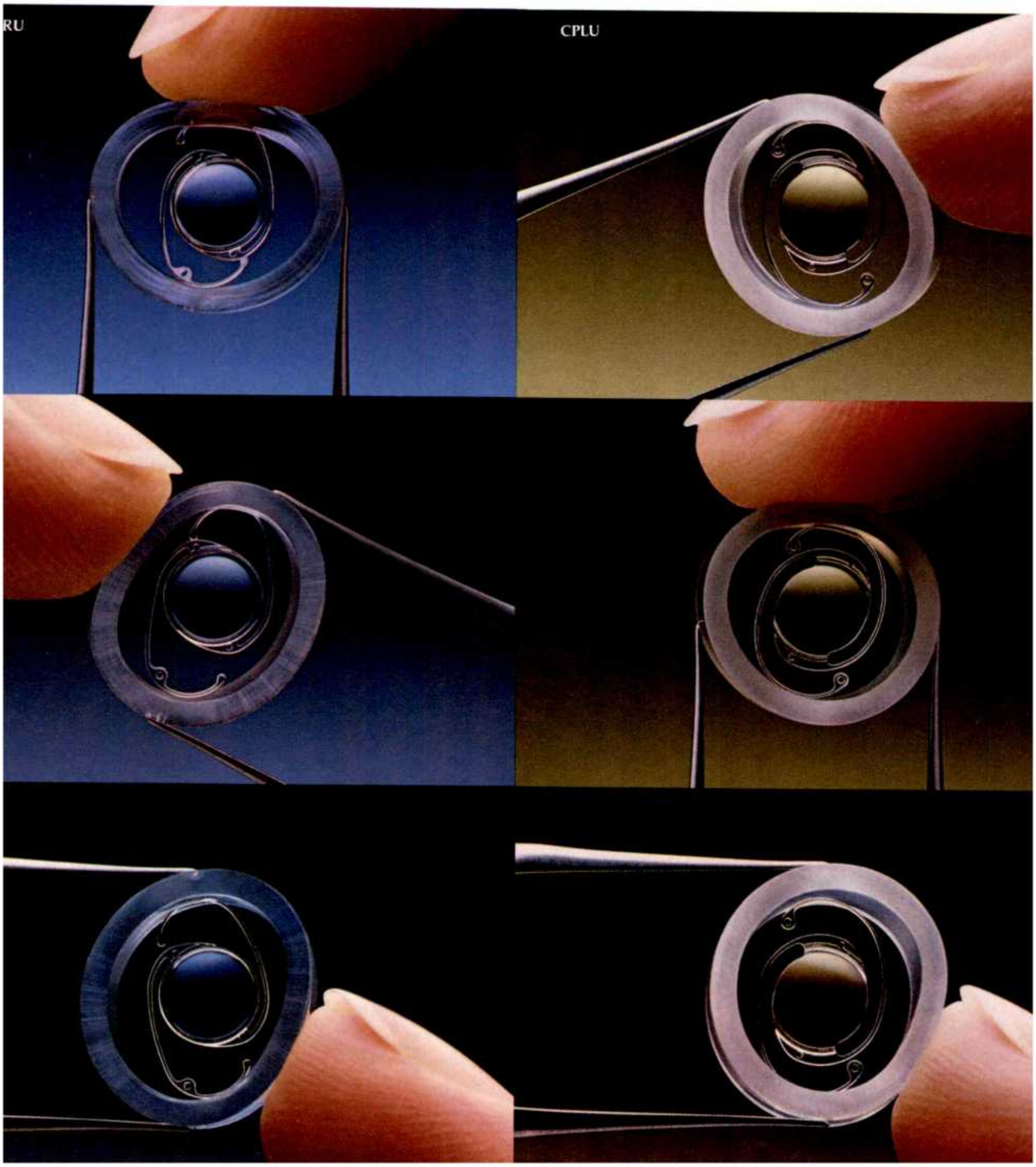

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British Journal of Ophthalmology, 1988, 72, 721–726

Prevalence and causes of blindness in the Northern Transvaal

PIUS J M BUCHER[1] AND CAREL B IJSSELMUIDEN[2]

From the [1]Department of Ophthalmology, Elim Hospital, and the [2]Department of Community Health, University of the Witwatersrand, Johannesburg and Elim Hospital, South Africa

SUMMARY During November 1985 a survey was carried out to determine the prevalence and causes of blindness in the Elim Hospital district of Gazankulu in the Northern Transvaal, South Africa, and to assess the Eye Department's effectiveness in preventing blindness. Using a random cluster sample technique, we screened 18 962 of the estimated 71 200 inhabitants of the district (26·6%). We found 109 blind people. The prevalence of blindness was 0·57% (95% confidence interval 0·46%–0·68%). The main causes of blindness were senile cataract (55%), corneal scarring due to trachoma (10%), uncorrected aphakia (9%), and open-angle glaucoma (6%). There were 14 aphakic blind persons who did not have aphakia glasses (43% of all persons operated on for cataract). Women had a significantly higher prevalence of blindness than men. After the age of 60 years the prevalence of blindness increased sharply. Women were 1·6 times less likely to have undergone cataract surgery than men. The two most effective steps to reduce the prevalence of blindness in the Elim district further are to provide aphakia glasses to all aphakic patients and to improve the accessibility of the Eye Department's surgical services.

The district served by the Elim Hospital is part of the Gazankulu 'homeland'. It is situated in the far northern part of the Transvaal Province of South Africa, just north of the tropic of Capricorn at an altitude of approximately 600 m above sea level. The summers are hot and winters are cool. The average rainfall is approximately 500 mm per year, 80% of which falls in the summer months.[1]

The Elim district's population is approximately 71 200 people.[12] The rate of natural increase is an estimated 3·0%, and 53·6% are younger than 15 years of age. Only 3·5% of the population are 65 years of age or older.[1] Owing to the migrant labour system over 70% of men in the economically active age groups are absent for most of the year.[3]

The population of the Elim district live in 21 well defined villages. Motorised transport is available but expensive. Water is scarce and must be collected from communal standpipes or rivers. The average cash income for a family of four persons is estimated at R50–150 per month. (The price of a month's supply of maize meal, the local staple food, is R40.) There is early and late childhood malnutrition, while there is no (anthropometric) undernutrition in adults.[45] It is estimated that 40% of women and 60% of men over the age of 20 years are literate.[1]

The ophthalmic services at the Elim Hospital have a long history.[6] The Ophthalmic Hospital at Elim is sufficiently equipped to deal with the diagnosis and treatment of most common eye conditions. Lid and orbit operations as well as extra and intraocular operations of the anterior segment can be performed.

The Elim Blindness Prevention Programme was started in 1972, and it consists of three interrelated activities. Preventive and promotive care is mostly provided by the volunteer Care Group (CG) members in all villages of the Elim Health Ward.[7] Curative care is given in the Eye Hospital and the mobile clinics by ophthalmologists and ophthalmic nurses. Rehabilitation is provided by an occupational therapist and a mobility trainer.[89]

Most information on the occurrence of blindness in Africa is based on hospital record reviews.[10 11] Hospital data are not likely to be representative of the pattern of eye diseases in a population, since geographical, cultural, socioeconomic, and political factors may all influence hospital usage.[11]

Available data on blindness in the Northern

Correspondence to Pius J M Bucher, MD, Augenspital, Mittlere Strasse 31, CH-4056 Basel, Switzerland

Transvaal is also limited. Earlier studies either were done more than 30 years ago[12 13] or were concerned only with a specific cause of blindness,[12] or were only hospital based.[9] Extrapolating from hospital records, Sutter estimated that blindness prevalence in the Northern Transvaal was 1·5–2·0%.[8 9]

The purpose of this study was to assess accurately the prevalence and causes of blindness in the Elim Health Ward. A secondary aim was to develop a hypothesis regarding the relation between the surgical activities of Elim's Eye Hospital and the prevalence of blindness in the Elim Health Ward. This last aim would have to be achieved without the availability of baseline data and without reference to a control area owing to the absence of prior community based research and lack of resources respectively. This study was conducted during November 1985.

Population and methods

Seven of the 21 villages in the Elim district (Fig. 1) were randomly selected, and all permanent residents (that is, excluding migrant workers) were included in the study sample.

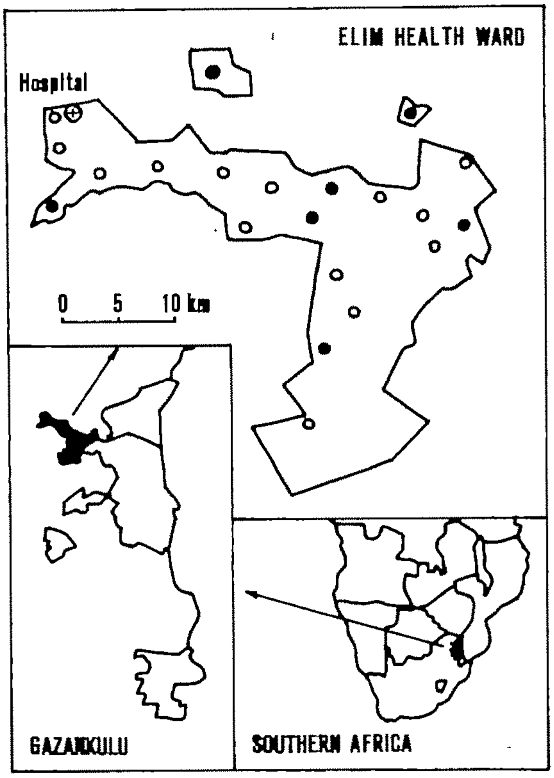

Fig. 1 *Composite map of the Elim district Study villages are indicated with solid dots.*

In the first stage of this survey CG members visited all houses in the seven selected villages. They checked the vision by asking people to count fingers at a distance of five large steps (this is always more than 3 meters) with both eyes open, wearing their own glasses (if any), outdoors in daylight. They also asked for persons who had had eye operations and for young children with 'problems of vision'. The names of all people who failed the finger counting test or had had eye surgery, and the names of all children with suspected vision problems, were recorded. Persons not present at the time of the CG member's visit were to be revisited on at least one occasion.

During the six weeks prior the survey the CG members were trained by hospital staff. Their competence was assessed by means of role plays. During the survey the CG members were supervised on a part-time basis.

In the second stage of the survey two to four days after completion of the screening the ophthalmic team (OT) visited the selected villages. The OT comprised an ophthalmologist, two ophthalmic nurses, a care group motivator, and an ambulance driver, and was based at a local school or clinic. To increase coverage further all local officials (teachers, headmen, clinic sisters, and community health workers) were also informed about the survey and were requested to bring anyone with suspected vision problems to the OT. All recorded, referred, and 'self-reporting' persons were screened by the OT. Persons whose names were recorded but who were not present at the time of the OT's visit were traced one or two days later. People who were not able to come to the OT were examined at their homes.

In this second screening phase people unable to count fingers at a distance of 3 meters (equivalent to visual acuity 3/60) or less were identified as blind.[14 15] These, together with all persons who had had an operation, constituted the final study group. Their personal and ophthalmic history was taken, and their socioeconomic status was assessed. The subject's visual acuity was tested for each eye, with and without correction, by Snellen charts. The anterior segment was examined with a torch and 5 times magnifying binocular glasses. The posterior segment was examined by direct ophthalmoscopy, and the intraocular pressure measured by Schiøtz tonometry. The visual acuity of aphakic eyes was determined with standard spheric correction, that is, +10, +11, or +12 dioptres.

Glaucoma was diagnosed by an intraocular tension above 21 mmHg and a glaucomatous excavation of the papilla. Owing to the limitations of the examination methods employed under field conditions we could differentiate only between open-angle (deep anterior chamber), narrow-angle (shallow anterior chamber, clinical signs of acute glaucoma attacks), and secondary glaucoma (trauma, cataract operation).

Classification of blinding diagnoses was done as recommended by the WHO.[14 15] The most probable cause of blindness for each eye was established as recommended by the National Society for the Prevention of Blindness in the USA.[16] Persons who had different causes of blindness for each eye were classified according to the most recent eye becoming blind.[16 17]

For reasons indicated in the discussion the study sample was treated as if it was the result of a random sampling procedure. The effects of clustering were therefore not taken into consideration when statistical calculations were done. Differences between two proportions were assessed by the standard formula. To assess differences in overall blindness prevalence in males and females, age adjusted rates were calculated from the total study sample as standard population. However, the male-female prevalence difference is not constant in all age groups, and the age adjusted rates are therefore only a crude measure of true prevalence.

In this article we differentiate between 'refractive' blindness, which is treatable by proper correction of the refractive error, and 'non-refractive' blindness, which includes all other causes of blindness. Effective blindness includes both 'refractive' and 'non-refractive' blindness.

Results

The estimated population of the seven selected villages combined was 18 962 persons, which is 26·6% of the total population of the Elim district.

The number of people identified by the CG members was 281, of whom 270 (96%) or more (some might have used other names) were subsequently seen by the OT. An additional 151 persons were referred by village officials or were self-reporting.

In total 172 people were included in the final study group, of whom 138 (80%) were identified by the CG. Of the 172 study subjects 109 were blind and 63 were not blind but had had an eye operation.

The prevalence of effective blindness in the Elim district was 0·57% (95% confidence interval 0·46%–0·68%). The prevalence of 'non-refractive' blindness alone was 0·50% (95% confidence interval 0·40%–0·60%).

Women were significantly more affected by blindness than men ($p<0\cdot0001$) (Table 1). The prevalence of blindness rose sharply after the age of 60 years in both sexes (Table 1). The average age of blind persons was 69·4 years (SD 15·3 years) The difference in the average age between males (65·2 years, SD 22·3 years) and females (71·1 years, SD 11·6 years) was not statistically significant.

The most common causes of bilateral blindness in the Elim district were senile cataract (55%), corneal scarring due to trachoma (10%), uncorrected aphakia after cataract surgery (9%), and open-angle glaucoma (6%) (Table 2). No proper diagnoses and

Table 1 *Distribution of population and blindness by age and sex*

Age group	*Population Elim Health Ward**				*Blindness*					
	Sex (%)		*Total*		*Cases*			*Prevalence (%)*		
	Males	*Females*	*n*	*(%)*	*Males*	*Females*	*Total*	*Males*	*Females*	*Total*
0–4	9·9	10·3	14377	20·2	1		1	0·05		0·03
5–9	9·1	9·1	12953	18·2						
10–14	7·6	7·6	10817	15·2	1		1	0·07		0·03
15–19	4·2	5·4	6830	9·6		1	1		0·10	0·06
20–24	1·6	4·7	4481	6·3	1		1	0·33		0·08
25–29	1·1	4·5	3982	5·6						
30–34	0·9	3·4	3057	4·3						
35–39	0·9	3·0	2772	3·9	1	1	2	0·60	0·17	0·27
40–44	0·8	2·4	2273	3·2	1		1	0·64		0·16
45–49	0·9	2·3	2273	3·2						
50–54	0·7	1·8	1775	2·5	1	3	4	0·69	0·89	0·83
55–59	0·7	1·7	1704	2·4	1	1	2	0·73	0·32	0·44
60–64	0·6	1·4	1419	2·0	1	8	9	0·85	3·18	2·43
65–69	0·5	0·8	921	1·3	4	16	20	4·23	10·91	8·31
70–74	0·4	0·6	707	1·0	4	16	20	5·60	12·78	10·14
75+	0·4	0·8	849	1·2	14	33	47	16·42	22·33	20·15
Total	40·5	59·5	71190	100·0	30	79	109			
Crude blindness prevalence								0·39	0·70	0·57
Age adjusted blindness prevalence								0·44	0·64	

*Excluding migrant workers. Institute of Development Studies [1]

Table 2 *Aetiology of blindness*

Aetiology WHO code, clinical entity	*Males*	*Females*	*Total*	*Percentage of all blindness*
Infection				
271 0 Corneal scar (trachoma)	1	10	11	10-09
369 0 Undefined blindness (both eyes) (trachoma)		1	1	0-92
Injury				
365.6 Secondary glaucoma (trauma)		1	1	0 92
377.1 Optic nerve atrophy (trauma)	1		1	0 92
369.0 Undefined blindness (both eyes) (trauma)	1	1	2	1·83
Neoplasm				
Systemic				
271.0 Corneal scar (vitamin A deficiency)	2	1	3	2·75
Degeneration				
371.4 Corneal, degeneration (cataract operation)		1	1	0 92
371 6 Keratoconus		1	1	0 92
366 1 Senile cataract	13	47	60	55·05
379 3 Aphakia (dislocation of the lens)		1	1	0-92
379 3 Aphakia (cataract operation)	4	6	10	9-17
363.4 Choroid degeneration	1	1	2	1·83
362.5 Drusen maculopathy	1		1	0-92
365.1 Open-angle glaucoma	4	3	7	6-42
379.2 Vitreous opacities (cataract operation)		2	2	1 83
Prenatal influence				
743.1 Microphthalmos	1		1	0 92
Cause not known				
360.4 Phthisis bulbi		1	1	0-92
271 0 Corneal scar	1		1	0-92
377.1 Optic nerve atrophy		1	1	0·92
369 0 Undefined blindness (both eyes)		1	1	0-92
Total	30	79	109	100

aetiology could be established in four persons (4%). In 41 blind persons (38%) a different aetiology in each eye was found. The relative importance of the causes of blindness was not affected by classification on eyes as compared with classification on persons.

The difference in prevalence of senile cataract between men and women was not statistically significant (p=0·14). Men were 1·6 times more likely to have been operated on for cataract (p=0·0455). Only 37% of persons blinded by senile cataract were operated on (Table 3). Blindness due to trachoma was virtually confined to women over the age of 65 years. Of all persons operated on for entropion 92% were women. The prevalence of blindness and the number of operations due to glaucoma was similar in males and females.

Table 3 *Distribution of blinding senile cataract and aphakia*

	Males (n=26)	*Females (n=64)*	*Total (n=90)*
Not operated on	13 50%	44 69%	57 63%
Operated (aphakic)	13 50%	20 31%	33 37%
Blind (with glasses)	0 0%	3 5%	3 3%
Not blind with glasses	11 42%	13 20%	24 27%
Have no glasses*	4 15%	9 14%	13 15%
Have own glasses	7 27%	4 6%	11 12%
Not blind without glasses	2 8%	4 6%	6 7%

*Three of these persons were classified with another cause of blindness than aphakia.

There were 17 study subjects who had had a cataract operation and were not blind, 14 with a previous entropion operation and seven with a previous glaucoma operation who were not blind in the operated eye but blind in the other eye. On the assumption that at the time of the survey these persons would have been blind without operation the total number of blind persons in our study sample would have been 147 and the blindness prevalence 0·77% (95% confidence interval 0·64%–0·90%). Compared with the actual blindness prevalence the effect of the ophthalmic surgical activities on the non-refractive and effective blindness prevalence in the Elim area has at best been a reduction of 26% and 35% respectively.

However, on the assumption that at the time of this study all persons at present blind from senile cataract, entropion (trachoma), and glaucoma would not have been blind if they had had eye surgery, the number of blind persons in our sample would have been only 20. The blindness prevalence would then have been 0·11% (95% confidence interval 0·06%–0·16%). Therefore only 30% of cases of blindness which could have been prevented or cured by an ophthalmic operation were in fact reached.

Discussion

To obtain reliable estimates of the blindness prevalence in the Elim population 18 962 people were screened. The screening of such a large number of people with only a few health professionals was possible only with the help of volunteer health workers (CG). The time and organisation needed to prepare them adequately for this survey forced us to keep the number of clusters to a minimum. Since the Elim district is relatively homogeneous in respect of population, geography, income distribution, and provision of health services, we do not think that the small number of clusters will compromise the results of the study. The results of this study are therefore probably representative of the whole Elim district.

The preparation time given to the CG was only six weeks, which is a relatively short time in the local context. In spite of this they identified 80% of all people included in this study. We cannot be certain how many blind people were not seen by the OT. We can only presume that the CG did visit all homes in their village and made follow-up visits to contact absentees. The respectability of the CG and the local health service in general make it unlikely that many blind persons were missed. Although the results of this study should technically be considered as 'minimum-estimates', we think that they are in fact a fair representation of the actual situation in the Elim district.

The blindness prevalence in the Elim district is lower than the prevalence in most other subSaharan African countries.[18–22] Differences in methodology between these studies and complete absence of onchocerciasis (in some African countries responsible for 12%–37% of all cases of blindness[18]) may partly explain this.

Blindness affects mainly those above 60 years of age, especially women. The excess risk of blindness in women is largely explained by blinding trachoma and untreated senile cataract. The reasons why blinding trachoma affects mostly women have been discussed earlier.[9] The lower literacy rate in women may explain the higher proportion of untreated senile cataract in women. The slightly higher average age of women may also be an explanation for the higher prevalence of degenerative diseases and diseases depending on repeated exposure to a noxious influence or agent.

Table 4 *List of five main causes of blindness in Elim district 1973 and 1985*

*1973** *Hospital based data*		*1985* *Population based data*	
Diagnosis	%	*Diagnosis*	%
Cataract	50	Cataract	55
Glaucoma	19	Trachoma	10
Trachoma	7	Aphakia/no glasses	9
Leukoma-staphyloma	5	Glaucoma	6
Corneal degeneration	3	Corneal scar (vitamin A deficiency)	3

*See Sutter.[9]

In 1973 a hospital based blindness study was done in the Elim area.[9] The one notable difference between causes of blindness in 1973 and 1985 is glaucoma (Table 4). The completely different methodology of the two studies might be the reason for this.

A surprise finding was that uncorrected aphakia after cataract surgery was the third most common cause of blindness. The reasons for this were not studied, but several factors might play a part, such as loss of glasses, inability to afford glasses, reasonable vision by the second eye at the time of first cataract surgery, or no need for glasses because of illiteracy and life style. To our knowledge it has not been reported earlier that uncorrected aphakia is a major cause of blindness. However, noting the similarities in health and health services between the Elim district and other third world areas, we would speculate that this cause of blindness may not be limited to the Elim district alone.

Surgical interventions by Elim Hospital's Eye Department have probably reduced blindness prevalence, but the effectiveness is low. One explanation might be the relative inaccessibility of the Eye Hospital's services. Geographical, economic, social, cultural, and political (borders) factors may all contribute to the inaccessibility.[23] The exact causes will have to be studied carefully, since it is clear from this study that the most significant contribution of Elim Hospital's Eye Department to the Blindness Prevention Programme in the short term is to operate on a much greater proportion of those people blinded by senile cataract and to provide aphakia glasses to all aphakic persons.

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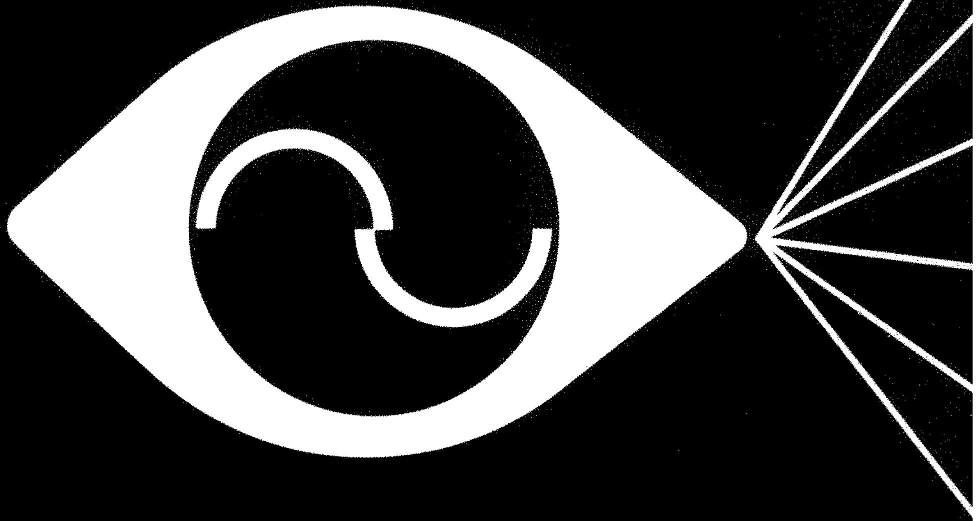

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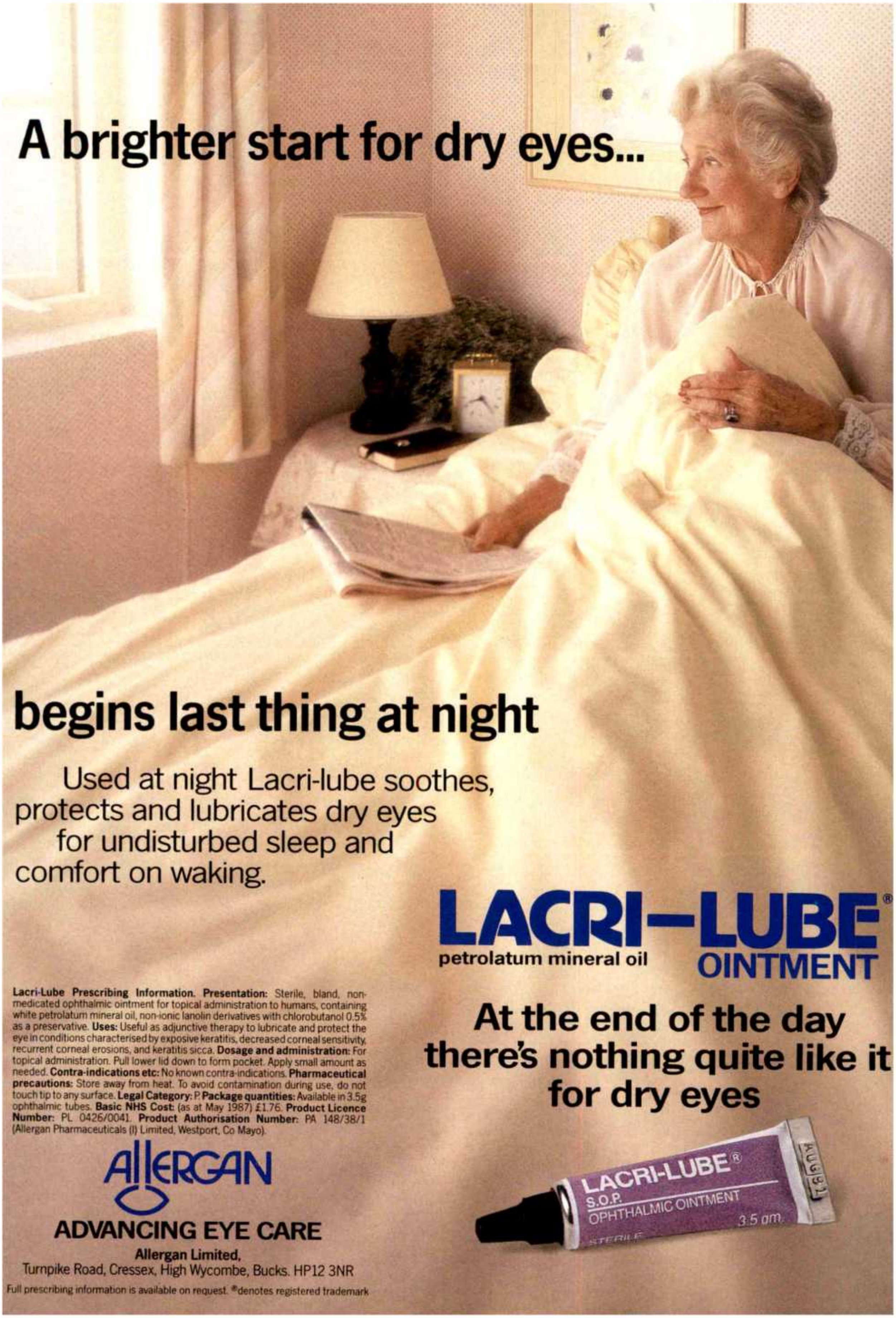

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Sickle cell retinopathy in Jamaican children: further observations from a cohort study

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SUMMARY Serial retinal examinations were performed in children aged 5 years and older and fluorescein angiography/angioscopy in children 6 years and older participating in a cohort study of sickle cell disease. There were 1229 patient years of observation among 389 children aged 5–13 years. Peripheral retinal vessel closure was present in approximately 50% of children with SS and SC genotypes at age 6 years and increased to affect 90% of children by age 12 years. A matched pair analysis, comparing groups with minimal and complete closure, indicated that complete closure was associated with significantly lower total haemoglobin and fetal haemoglobin levels and significantly lower weight in SS disease, whereas in SC disease the risk factors appeared to be high mean cell volume and low platelet count. Proliferative retinopathy was rare, occurring only once in an 8-year-old boy with SC disease, despite 592 patient years of observation in children over this age.

The vaso-occlusive process of sickle cell disease affects the retinal vasculature, resulting in both non-proliferative and proliferative manifestations. The patterns, natural history, and risk factors for these changes have been extensively studied, but generally in patients presenting clinically with relatively advanced retinal disease. The early development of vascular changes, their risk factors, and their relationship to the formation of proliferative sickle retinopathy (PSR) remain largely unknown. A cohort study has provided a representative sample of children with sickle cell disease, and observations on the early development of ocular changes are reported.

Materials and methods

The children were part of a cohort study of sickle cell disease based on the screening of 100 000 consecutive normal deliveries at the main Government Maternity Hospital (Victoria Jubilee Hospital). Between June 1973 and December 1981 this programme detected 315 children with homozygous sickle cell (SS) disease, 201 with sickle cell-haemoglobin C (SC) disease, 33 with sickle cell-beta$^+$ thalassaemia (S beta$^+$ thal) and 14 with sickle cell-beta^0 thalassaemia (S beta^0 thal). The diagnostic procedures[1] and the methods of review[2] have been reported.

Visual acuity was assessed as best corrected vision with Snellen's type or an illiterate E chart. Ophthalmoscopy through a dilated pupil was routinely performed in children aged 5 years and over Fluorescein angiography/angioscopy was routinely performed in children aged 6 years and over unless ophthalmoscopy revealed changes requiring fluorescein study at an earlier age.

At the date of last assessment (January 1986) the children were aged 5–13 years. Retinal examinations had been performed at least once in 219/242 (90%) eligible children with SS disease, in 135/162 (83%) eligible children with SC disease, in 24/30 (80%) children with S beta$^+$ thalassaemia, and in 11/12 (92%) children with S beta^0 thalassaemia. Of these, fluorescein angiography/angioscopy had been performed at least once in 189/219 (86%) with SS disease, in 124/135 (92%) with SC disease, in all children with S beta$^+$ thalassaemia, and in 9/11 (82%) children with S beta^0 thalassaemia. The numbers of

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children with S beta$^+$ thalassaemia and S beta^0 thalassaemia were too small to draw conclusions on the risk factors for retinal pathology in these genotypes, and this report is therefore confined to children with SS and SC disease.

Peripheral retinal vessel closure was diagnosed if there was continuing retinal non-perfusion extending posteriorly from the ora to at least the equator. The posterior extent of presumed closure proved too difficult to measure more accurately. The circumferential extent of closure was arbitrarily classified as minimal (less than 60° closure in each eye), extensive (combined closure in both eyes exceeding 360°), and complete (entire periphery of both eyes affected).

Haematological indices were measured, as previously described, by means of electronic counters (Coulter Electronics). Fetal haemoglobin (HbF) was measured by alkali denaturation.[3] Alpha thalassaemia was detected by restriction endonuclease analysis of DNA obtained from the buffy coat.[4] Since the distributions of HbF and reticulocytes were skewed, the transformations $\log_e$ (HbF+4) and $\log_e$ (reticulocytes+1) were used to give a more normal distribution prior to analysis.

Results

VISUAL ACUITY

The proportion of children with normal visual acuity (better than 6/12) increased with age, 57% at 5 years, 62% at 6 years, 71% at 7 years, 78% at 8 years, 77% at 9 years, to 80% at 10 years, most probably reflecting greater understanding and co-operation.

A visual acuity of 6/12 or less was observed in at least one eye on one or more occasions in 17 children (12 SS, 5 SC). A child with acuity of less than 6/60 had had pneumococcal meningitis with bilateral metastatic endophthalmitis and extensive chorioretinal atrophy. In two children acuities of 6/36 were attributed to anisometropic amblyopia and to albinism. In the others (three children with 6/18, 11 with 6/12), which were generally observed on only one occasion, no cause could be found.

RETINAL PATCHES

Retinal patches were circumscribed areas of discolouration in the peripheral retina generally with well defined borders. They were frequently but not always related to obvious vessels, and usually appeared in the plane of the retina. Some were darker and some lighter than the surrounding retina, probably representing the signs previously described as dark-without-pressure[5] and white-without-pressure.[6] Some were grey-brown with iridescent spots resembling the previously reported mottled brown areas.[7] These were probably the sequel to intraretinal haemorrhage, though recent haemorrhages were seen infrequently.

These retinal patches occurred in a similar proportion of children with SS and SC disease and increased significantly ($p<0.05$) from 20% at 5 years to 47% at 10 years in both genotypes combined. Between the ages of 6 and 10 years they were significantly ($p<0.05$) more frequent in males in both genotypes. Analysis of the circumferential distribution of patches revealed a significant preponderance (65%) on the temporal side.

PERIPHERAL RETINAL VESSEL CLOSURE

Prevalence. Fluorescein angiography was not performed before the age of 6 years unless retinal examination indicated abnormalities, so the proportion of children with closure is probably over-represented at both ages 5 (range 4·5–5·4 years) and 6 (range 5·5–6·4 years). From age 7 years data are more representative, and the proportion of children showing either some closure or extensive closure on angiography increased between 7 and 12 years in both SS and SC disease (Fig. 1).

Closure was more common in SS than in SC disease between the ages 6 and 11 years and extensive closure

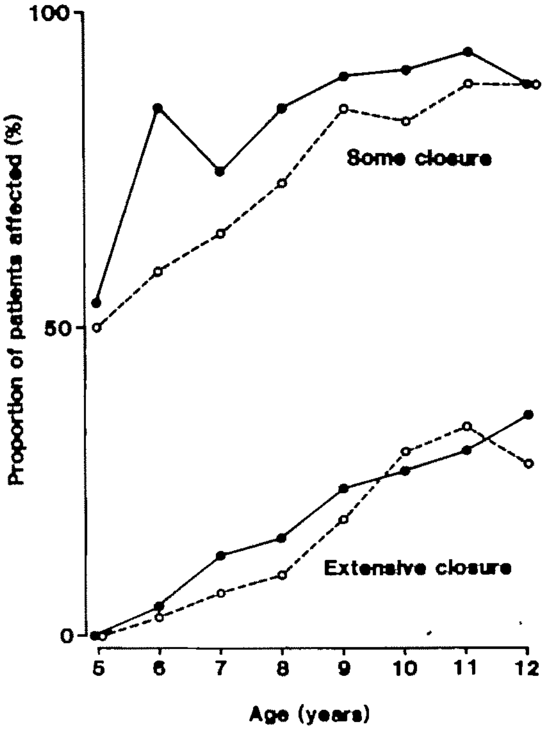

Fig. 1 *Prevalence of peripheral retinal vessel closure at different ages in SS (●—●) and in SC (○—○) disease.*

from age 6 to 9 years, though the differences did not reach statistical significance. Closure was more common in males in both SS and SC disease between the ages of 6 and 10 years, the sex difference within both genotypes being significant ($p<0\cdot05$) at 7 years but not at later ages. The degree of closure in both eyes was generally similar, a difference in circumferential grading of 120° or more between eyes occurring in only 42/189 (22%) patients with SS disease and in 25/124 (20%) patients with SC disease.

Complete closure had occurred in 23 SS children (14 male, 9 female) and in 16 SC children (13 male, 3 female). There was a preponderance of males among those with complete closure, the Mantel Haenszel χ^2 test indicating a significant difference in SC disease ($\chi^2=5\cdot44$, $p<0\cdot05$) but not in SS disease ($\chi^2=0\cdot41$). The overall χ^2 test for sex, taking account of genotype was significant ($\chi^2=4\cdot64$; $p<0\cdot05$).

Incidence. Closure was present on first examination in 137/189 (72%) SS children and in 68/124 (55%) SC children, so that only the remaining 52 SS and 56 SC children were available for prospective observations on the initial incidence of closure. In these cases closure was observed to develop for the first time in 29 SS and in 34 SC children between the ages of 7 and 12 years, the incidence being approximately constant across the age span and of a simliar order in both genotypes. At the last examination there was no closure in 23 children with SS disease (seven aged 10 years and over) and in 22 children with SC disease (eight aged 10 years and over).

Progression. Observations on the progress of closure were possible in all patients who had not attained complete closure, and annual assessments were possible over 325 patient years in SS disease and over 191 patient years in SC disease. Closure generally progressed gradually over several years from none to complete closure. Among a total of 118 patient years of observation commencing with no closure five patients (two SS, three SC) developed extensive closure within one year, and one of these, an SC male aged 7 years, progressed to complete closure. This rapid closure was not associated with dramatic clinical events and the child progressing to complete closure within one year appeared to be well throughout the year's observation.

Risk factors for closure. The possible role of some haematological and clinical features as determinants of closure was assessed in a matched pairs analysis comparing groups with complete closure and with none or minimal closure. There were 19 pairs of children with SS disease and 13 pairs with SC disease, all matched to within six months of age and having steady state haematology recorded within six months of the ophthalmological examination.

Patients with SS disease and complete closure had significantly lower levels of total haemoglobin and HbF (Table 1). Although earlier observations[4] had suggested that the effect of haemoglobin was dependent on the effect of HbF, analysis of variance in this study indicated independent effects of both total haemoglobin and HbF. Patients with SC disease and complete closure had higher mean cell volumes (MCV) ($p<0\cdot05$) Weight was significantly lower among SS patients with closure, but there were no differences in height in either genotype (Table 2).

There were nine patients with SS disease and homozygous alpha thalassaemia, four of whom had no closure at last examination (ages 7, 8, 10, and 12 years). Analysis at age 7 years, when data were

Table 1 *Comparison of some haematological features in matched pairs of patients showing either minimal or complete peripheral retinal vessel closure*

	Minimal (<60°) or no closure		*Complete closure*		*Significance*	
Variable	*Mean*	*SD*	*Mean*	*SD*	*t*	*p*
SS disease (n=19 pairs)						
Haemoglobin (g/dl)	8·4	1·2	7·2	0·8	−3·91	<0·001
Log_e (HbF+4)	2·38 (6·8)	0·41	2·00 (3·4)	0·30	−3·77	<0·001
MCHC (g/l)	34·6	3·2	34·5	2·8	−0·11	NS
MCV (fl)	83·7	8·0	83·5	7·5	−0·09	NS
Log_e (retics+1)	2·29 (8·9)	0·49	2·53 (11·6)	0·34	1·43	NS
Platelets ($\times10^9$/l)*	413	158	400	149	0·19	NS
SC disease (n=13 pairs)						
Haemoglobin	10·7	1·4	10·8	0·9	0·37	NS
Log_e (HbF+4)	1·66 (1·3)	0·25	1·63 (1·1)	0·23	0·34	NS
MCHC (g/l)	35·1	2·0	35·5	1·8	0·47	NS
MCV (fl)	74·3	8·9	79·4	6·9	2·07	<0·05
Log_e (retics+1)	1·71 (4·5)	0·34	1·68 (4·4)	0·42	−0·28	NS
Platelets ($\times10^9$/l)†	390	116	191	78	5·07	<0·01

*Based on 11 pairs †Based on five pairs

Figures in parentheses represent means re-expressed in original units.

Table 2 *Heights and weights in matched pairs of patients showing either minimal or complete peripheral retinal vessel closure*

	Minimal (<60°) or no closure		*Complete closure*		*Significance*	
Variable	*Mean*	*SD*	*Mean*	*SD*	*t*	*p*
SS disease						
Age (years)	9·4	1·7	9·5	1·7	–	–
Weight (kg)	25·2	3·8	23·3	3·7	−2·72	<0·05
Height (cm)	129·8	8·9	128·8	8·9	1·48	NS
SS disease						
Age (years)	9·8	1·3	10·0	1·4	–	–
Weight (kg)	25·7	4·3	27·5	4·7	1·09	NS
Height (cm)	131·0	9·6	135·4	9·2	1·31	NS

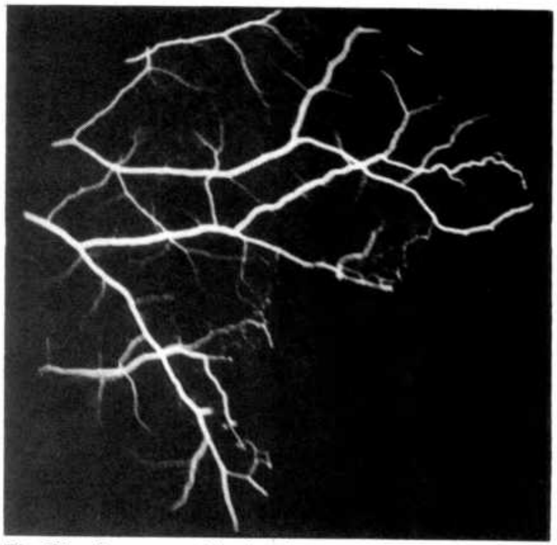
Fig. 2B *Same area eight days later reveals spontaneous cessation of perfusion.*

available on 6/9 patients with homozygous alpha thalassaemia, indicated that these patients were more likely to have normal eyes or minimal closure than those with a normal alpha globin gene number (Fisher's exact test, p=0·01). In SC disease the two patients with homozygous alpha thalassaemia had less closure, but the difference was not significant.

Proliferative retinopathy. A boy with SC disease is the only child with PSR to date. When assessed at ages 6 and 7 years he had peripheral retinal vessel closure in both eyes, more marked in the left. At 8½ years closure had extended in the right eye and there was a circumscribed leaking lesion (Fig. 2A) in the left temporal periphery at 4 o'clock. When he was reassessed eight days later perfusion had ceased (Fig. 2B). At 9 years closure had progressed to 360° of both eyes, and the PSR lesion in the left periphery was reperfused and more extensive (Fig. 2C). At age 10 years this lesion had enlarged further (Fig. 2D) and PSR had developed in the other eye.

Discussion

The patient co-operation necessary for fluorescein angiography restricted its routine use until 6 years, by

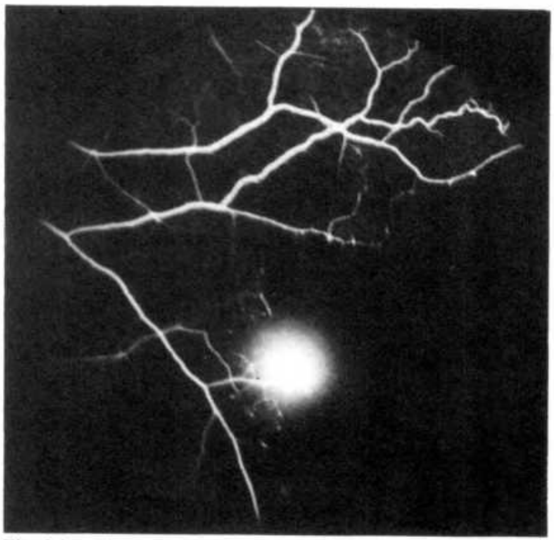
Fig. 2A *Fluorescein angiogram of the left temporal periphery in an 8½-year-old male with SC disease showing small leaking PSR lesion.*

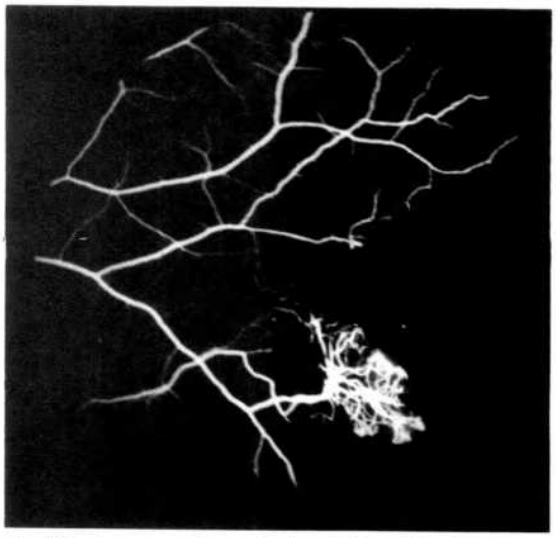
Fig. 2C *Same area six months later indicated the PSR lesion is reperfused and has extended.*

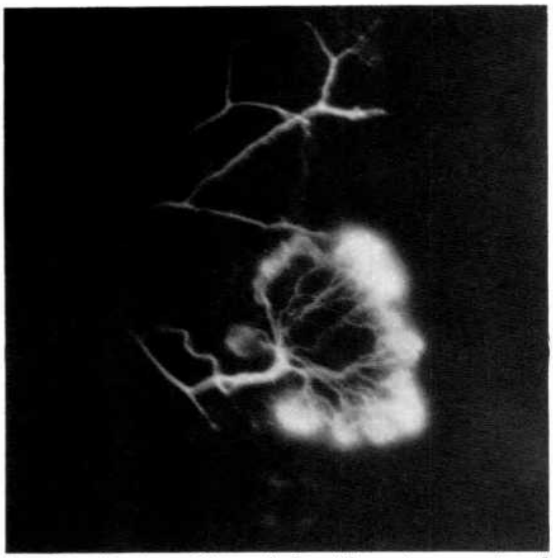

Fig. 2D *Same area 18 months later illustrating extension of the PSR lesion.*

which age over half of the study children had already developed peripheral retinal vessel closure. In these cases it was possible to make some observations on the progression of closure, and in the others the development of closure for the first time could be observed.

Age was a major determinant of retinal vessel occlusion, which generally manifested a steady progression, dramatic changes within one year being uncommon. Males of both genotypes were at significantly higher risk for developing retinal patches and vessel occlusion, although the mechanism was not clear. Total haemoglobin levels are significantly lower in males than in females with SS disease from ages 5 to 14 years,[9] and males have slightly lower HbF levels,[10] both indices being risk factors for closure in the matched pairs analysis. The significance of genotype, with an increased risk of closure in SS disease observed in an earlier study,[8] was less apparent in the present more extensive data.

Matched pairs analysis indicated that a low total haemoglobin and low HbF were risk factors for complete closure in SS disease. A low HbF is generally associated with evidence of increased intravascular sickling[11] and has been incriminated in several vaso-occlusive complications in SS disease. The association of closure with a low total haemoglobin, although consistent with previous retinal observations,[8] conflicted with observations in other presumed vaso-occlusive sequelae of SS disease. Thus avascular necrosis of the femoral head,[12] proliferative sickle retinopathy,[13] and painful crises[14] all appear more common with *high* total haemoglobin levels, especially in association with a low HbF. A positive relationship between total haemoglobin and HbF[15] suggests that the apparent effect of low total haemoglobin may be accounted for by the effect of a low HbF. Analysis of variance indicated that this was indeed the case in an earlier study,[8] but the present data suggested an effect of low haemoglobin independent of the low HbF. Homozygous alpha thalassaemia, though uncommon and affecting only 3% of the Jamaican population, appeared to protect against retinal vessel closure. This subdivision of SS disease is associated with a lowered intracellular haemoglobin concentration, consequent inhibition of sickling, a lower haemolytic rate, and an increased total haemoglobin level. The clinical consequences are not uniformly beneficial, but the current study suggests that homozygous alpha thalassaemia may be beneficial to peripheral retinal blood flow at this age.

Analysis of haematological risk factors in SC disease indicated that a high MCV and low platelet counts were significantly associated with complete closure. Both findings were unexpected and difficult to explain. Homozygous alpha thalassaemia may also protect against retinal closure in SC disease, though the effect failed to reach significance with the two patients available in this study.

The significance or pathological basis of retinal patches is not clear, though their coincident distribution with that of peripheral vaso-occlusion suggests that they may be the sequel to vaso-occlusive events. Pre- or intraretinal haemorrhages were occasionally observed to evolve into patches, so some if not all may represent schisis cavities or other sequelae of haemorrhage. It is well recognised that arteriolar occlusions may be transient and subsequent reperfusion be followed by extravasation of blood through the damaged arteriolar wall and a local retinal haemorrhage. In several patients with arteriolar occlusion in the present study, perfusion was re-established without any detectable permanent damage in the peripheral capillaries. If arteriolar obstruction causes closure, it seems likely that recurrent occlusion may be necessary before permanent reduction of the capillary bed occurs. In the majority of children the peripheral vasculature was remarkably stable, with little evidence of the remodelling reported in adults.[16]

This hypothesis of a dynamically changing pattern of transient occlusion and reperfusion may explain the relatively slow development of PSR. Only one child, aged 8 years with SC disease, has developed PSR out of a total of 592 observations in patients aged 8 years and over. Even this patient demonstrated the transient perfusion of early PSR, though the abnormal vessels were reperfused and extended when seen one year later. It may be anticipated that the children in the cohort study are shortly to enter the period of rapid progression.

We thank Dr Douglas Higgs, of the MRC Molecular Haematology Unit in Oxford, for ascertainment of the alpha thalassaemia status of these children. The work was supported in part by the Wellcome Trust and in part by Comprehensive Sickle Cell Grant PHS HL 15168 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland

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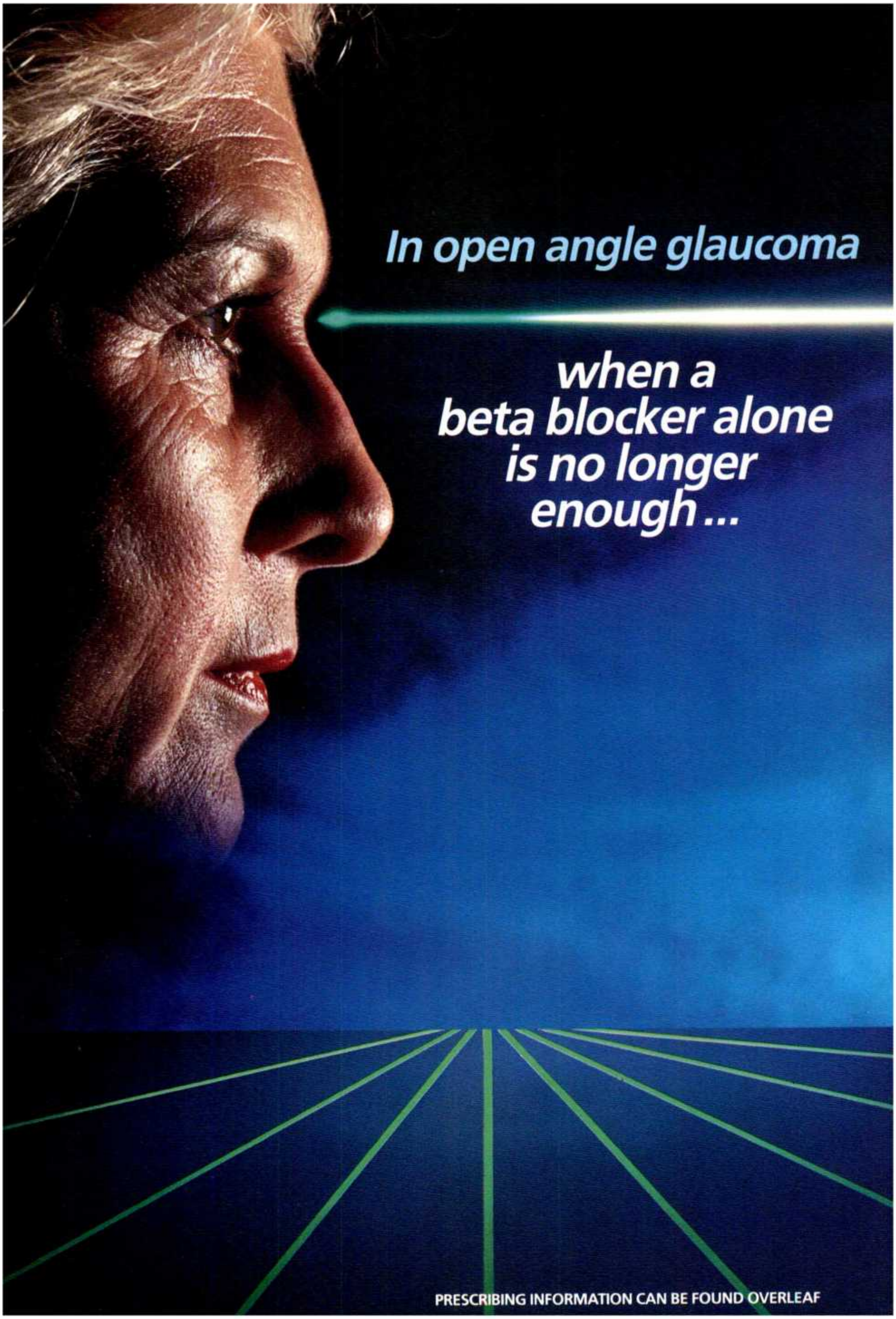
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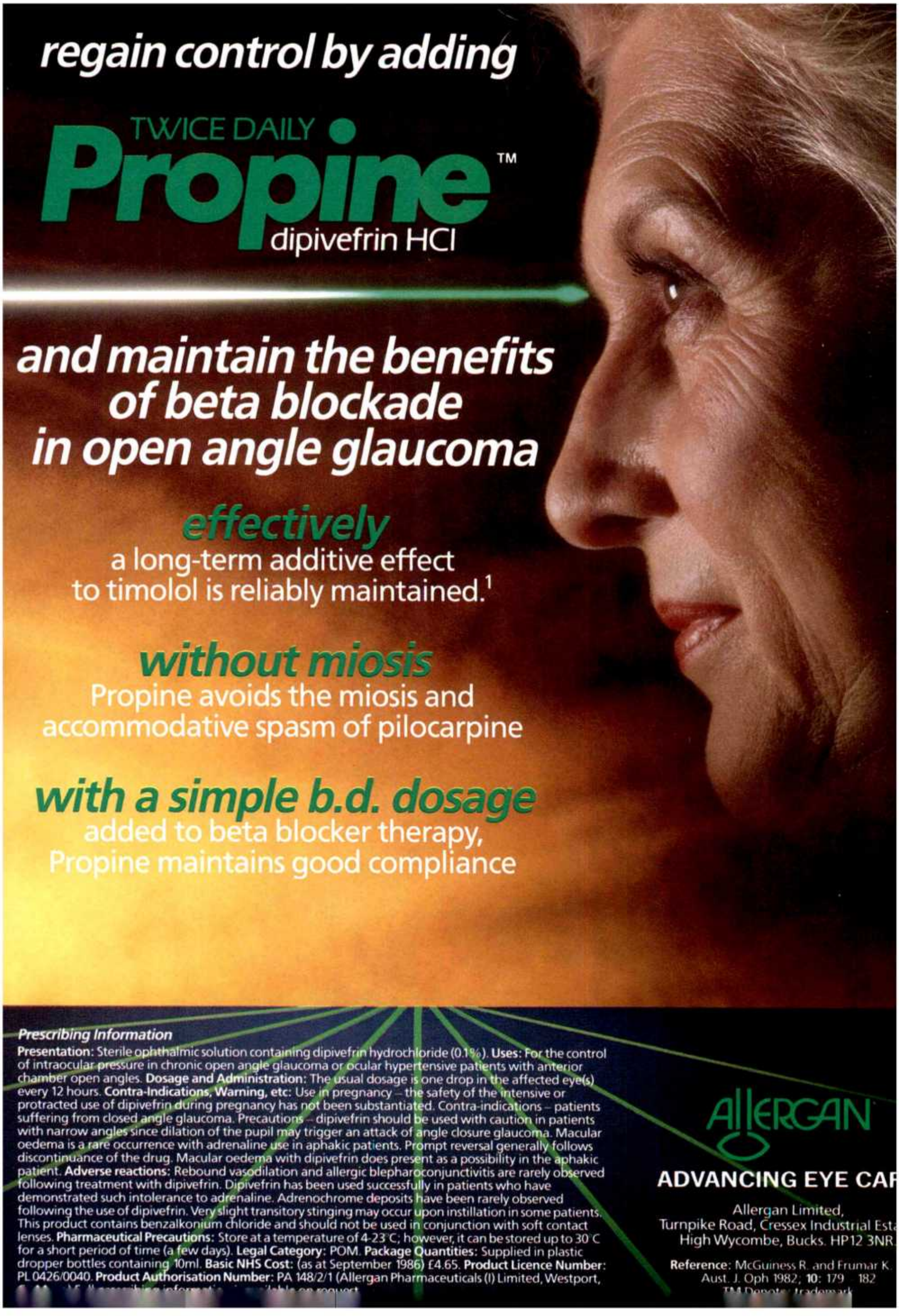

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British Journal of Ophthalmology, 1988, **72**, 733–736

How do general practitioners manage eye disease in the community?

P J McDONNELL

From the Department of Ophthalmology, St Thomas's Hospital, London

SUMMARY A survey of the management of eye disease in the community was carried out in two general practices over a three-month period. During this time there were 238 consultations by patients with ocular symptoms, making up 2·3% of all consultations and giving an annual consultation rate for eye disease of 66 per 1000 persons at risk. The four commonest diagnoses were bacterial conjunctivitis, allergic conjunctivitis, meibomian cyst, and blepharitis, and these accounted for more than 70% of the consultations. A variety of topical and systemic treatments were used, with topical chloramphenicol prescribed in 55% of consultations. Referral to a hospital eye department resulted from 35 consultations, giving a referral rate of 15% of all consultations.

There are few detailed studies assessing the way in which general practitioners manage eye disease in the community. The most comprehensive data in this country on prevalence of eye disease come from the morbidity statistics of the Royal College of General Practitioners.[1] However, their classification of eye disease is into broad categories: for instance there is no differentiation between the two common conditions of bacterial conjunctivitis and allergic conjunctivitis, and there is no assessment of the management of eye diseases by general practitioners.

Ophthalmologists are increasingly aware of the importance of primary ophthalmic care in the community. An improvement in both undergraduate and postgraduate teaching of ophthalmology is vital to help the general practitioner to become more confident in the diagnosis and management of the wide range of eye diseases found in general practice.

An assessment of how general practitioners treat eye disease in the community at present might help in planning future teaching. This survey was carried out over three months in two general practices in South London. The aims of the survey were to determine the prevalence of eye diseases in the two general practices and to determine how these diseases were treated by the general practitioners.

Subjects and methods

The survey was carried out for the three months July 1986 to September 1986 in two general practices. One practice consisted of four general practitioners in Clapham, South London, with a practice population of 9521 patients. The other practice consisted of three general practitioners in Streatham, South London, with a practice population of 4880 patients, making a total study population of 14 401. Analysis of the practice populations by age shows that 87% were under 65, 7% were 65 to 74, and 6% were 75 or older. This breakdown reflects the nature of the two practice areas, with fewer old people than the national average and a large number of working people, both single and married, in the 25–44 age group.

All consultations of patients with ocular symptoms were with general practitioners. A special form was used to record the presenting symptoms, the diagnosis made by the general practitioner, and the subsequent management including details of drug treatment and any referral.

Results

During the period of the survey there were 238 consultations by 224 patients with ocular symptoms, representing 2·3% of the total number of medical consultations, which was 10 182. This gives a consul-

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tation rate of 16·5 per 1000 persons at risk for the period of the survey and an annual consultation rate for patients with ocular symptoms of 66 per 1000 persons at risk.

The age and sex distribution of the patients consulting with ocular symptoms is shown in Table 1. The most frequent attenders were in the 0-4 years and 25-44 years age groups, each representing 26% of the total. Only 15% of the patients consulting with ocular symptoms were aged 65 or over.

The general practitioners made a range of 29 diagnoses in the 238 consultations, shown in Table 2 in order of frequency. Bacterial conjunctivitis was the commonest diagnosis, accounting for 44%, allergic conjunctivitis for 15%, meibomian cyst for 8·4%, and blepharitis for 5·4%. Problems with contact lenses were diagnosed in 4·2%, while corneal abrasions and foreign bodies accounted for 3·4% of consultations.

The majority of patients were managed by the general practitioners without referral to a hospital eye department. Table 3 shows the wide range of treatments used. The commonest treatment was topical chloramphenicol, prescribed in 55% of consultations. Treatment for allergic conjunctivitis was the next most frequent, with topical sodium cromoglycate being prescribed in 8% of consultations and oral antihistamines in 4·6%. Only seven consultations (2·9%) resulted in the prescription of topical steroids. No treatment was given in 46 consultations, representing 19·3% of the total; of these patients some were referred to the hospital eye department and some received advice only.

Referral to a hospital eye department resulted from 35 consultations, giving a referral rate of 15%. Of these 35 patients two had been sent by an optician to their general practitioner with a form GOS 18 recommending referral to the local eye department. The diagnoses made by the general practitioners in the patients referred to hospital are shown in Table 4. The diagnoses made by the general practitioners in the two patients sent by opticians to be referred to hospital were chronic glaucoma and reduced visual acuity.

Table 1 *Age and sex of patients consulting with ocular symptoms*

Age (years)	*No (%) of patients*
0–4	58 (26)
5–14	29 (13)
15–24	25 (11)
25–44	58 (26)
45–64	20 (9)
65–74	25 (11)
75 and over	9 (4)
Male	94 (42)
Female	130 (58)

Table 2 *Classification and frequency of ocular diagnoses made by general practitioners*

Disease	*No (%) of diagnoses*
Bacterial conjunctivitis	104 (44)
Allergic conjunctivitis	35 (15)
Meibomian cyst	20 (8·4)
Blepharitis	13 (5·4)
Problems with contact lens	10 (4·2)
Corneal abrasion and foreign body	8 (3·4)
Stye	7 (2·9)
Floaters	6 (2·5)
Blocked nasolacrimal duct	5 (2·1)
Dacryocystitis	4 (1·6)
Irritability of eyes	3 (1·3)

2 cases each of squint, iritis, spontaneous subconjunctival haemorrhage, amaurosis fugax, twitching eyelid, sebaceous cyst, ingrowing eyelash, and chickenpox lesions on eyelid

1 case each of chronic glaucoma, angioneurotic oedema, ectropion, episcleritis, cataract, lid eczema, vitreous haemorrhage, retinal detachment, and pterygium

Table 3 *Treatments given by general practitioners*

Treatment	*No (%) of patients*
Topical chloramphenicol	133 (55)
Topical sodium cromoglycate	19 (8)
Oral antihistamines	11 (4·6)
Oral antibiotics	9 (3·8)
Topical steroids	7 (2·9)
Topical antihistamines	7 (2·9)
Topical gentamicin	5 (2.1)
Topical hypromellose	2
Hot spoon bathing	2
Lid cleaning	1
Lash removed	1
Massage lacrimal sac	1
No treatment, advice only	46 (19·3)

Table 4 *Diagnoses made by general practitioners in patients referred to hospital eye department*

Diagnosis	*No of patients*
Corneal abrasion and foreign body	5
Floaters	4
Meibomian cyst	4
Squint	2
Iritis	2
Amaurosis fugax	2
Sebaceous cyst	2

1 case each of chronic glaucoma, episcleritis, cataract, ingrowing eyelash, lid eczema, blepharitis, conjunctival haemangioma, blocked nasolacrimal duct, retinal detachment, vitreous haemorrhage, dacryocystitis, reduced visual acuity, 'shimmering' in eyes, and scars from previous squint surgery

Discussion

Studies of patients with ocular symptoms in general practice have tended to limit their inquiries to the prevalence of eye disease. The most extensive survey in this country is that organised by the Royal College of General Practitioners. In the report on 1981-2 morbidity statistics from general practice[1] the results from a year-long survey gave an annual consultation rate for patients with eye disease of 70·1 per 1000, representing 2·06% of all medical consultations. More recently an ophthalmologist carried out a three-month study at a community health centre and found an annual consultation rate of 57 per 1000, representing 2·7% of all consultations.[2] These figures are comparable with this three-month study, where the consultation rate was 66 per 1000, representing 2·3% of all consultations.

The Royal College of General Practitioners study is of more limited value in reviewing the range of conditions seen by general practitioners, as there are only 12 categories of diagnoses, and common conditions such as bacterial conjunctivitis and allergic conjunctivitis are included under the one heading of conjunctivitis. The three commonest diagnoses were conjunctivitis, meibomian cyst, and blepharitis, which are the same three as in the present study.

The study by Dart,[2] which took place between the months of May and August, has allergic conjunctivitis as the commonest diagnosis, accounting for 21% of cases, while bacterial conjunctivitis accounts for only 4·7% of patients seen by the ophthalmologist in the community. This contrasts with the present study, which also took place in the summer, where bacterial conjunctivitis accounts for 44% of cases and allergic conjunctivitis accounts for 15% of cases. Interestingly in Dart's study, when patients saw only the general practitioner, the diagnosis of bacterial conjunctivitis was more likely, being made in 39% of cases. It could be that general practitioners overdiagnose bacterial conjunctivitis at the expense of other diagnoses: the ophthalmologist had a slit-lamp in the surgery, which made more detailed examination possible. It may also be that the patients seen by the ophthalmologist were a selected group, as some patients who saw a general practitioner then declined a further visit to see the ophthalmologist.

As both Dart's study and the present study were carried out during the summer months, the prevalence of allergic conjunctivitis is likely to have been higher than at other times of the year and thus possibly have influenced the overall consultation rates. However, extrapolation of the three-month results from both studies gives annual consultation rates very similar to those reported in the Royal College survey.

The chronic conditions of glaucoma and cataract were infrequently diagnosed in the present study — only one case of each in the three month period. This contrasts with the Royal College study, where cataract and glaucoma together accounted for 7·6% of diagnoses. There are two factors which may explain this discrepancy. The practice areas studied had a lower percentage of patients over 64 (13%) than the national average of 15%. In addition there is easy access to hospital eye casualty and clinic services in the area, which may reduce the number of consultations with general practitioners for cataract and glaucoma.

Only two recent studies mention the treatment used by general practitioners in the management of eye diseases. A year-long Australian study found that chloramphenicol was the commonest antibiotic used for infective problems, but no figures are given.[3] That study also found that topical steroids were occasionally prescribed, but again no figures are given. A recent postal survey carried out in this country asked general practitioners about their management of the red eye.[4] Topical chloramphenicol was used by 93% of the respondents to treat infective conjunctivitis, but for non-specific conjunctivitis 10% chose a steroid-containing preparation. This survey, however, asked only about prescribing intentions and was not a retrospective study of patient management. The general practitioners in the present study treated patients with a fairly limited range of drugs. Chloramphenicol was the most popular antibiotic used topically.

The most frequent treatment for allergic conjunctivitis was sodium cromoglycate. In view of a recent editorial[5] and the study by Lavin and Rose[6] it is interesting to note that 2·9% of patients were treated with topical steroids. These patients were mainly suffering from allergic conjunctivitis that had not responded to topical sodium cromoglycate. No patients were treated with combined steroid and antibiotic prescriptions.

The referral rate for patients in the study was 15% of all consultations and was for a wide range of diagnoses. The Royal College survey does not record the referral rate for patients with ocular symptoms, but the overall referral rate for all diseases and conditions is 16·5%, which is comparable to the rate in this survey.

This study has shown that general practitioners successfully manage a wide range of eye diseases in the community. The diseases they see may be divided into two groups: common external eye conditions such as conjunctivitis and meibomian cyst, which are not sight threatening and are relatively easy to treat in the community, and secondly rare but sight threatening conditions such as retinal detachment and glaucoma, which must be referred to a hospital eye department.

Patients were treated by their general practitioners with a limited range of drugs the majority of which could be used safely in the community. Teaching of medical students and update of general practitioners should do more to emphasise the two broad groups of patients with eye disease in the community and to encourage the use of a limited range of safe topical medications in the treatment of patients with eye disease in general practice.

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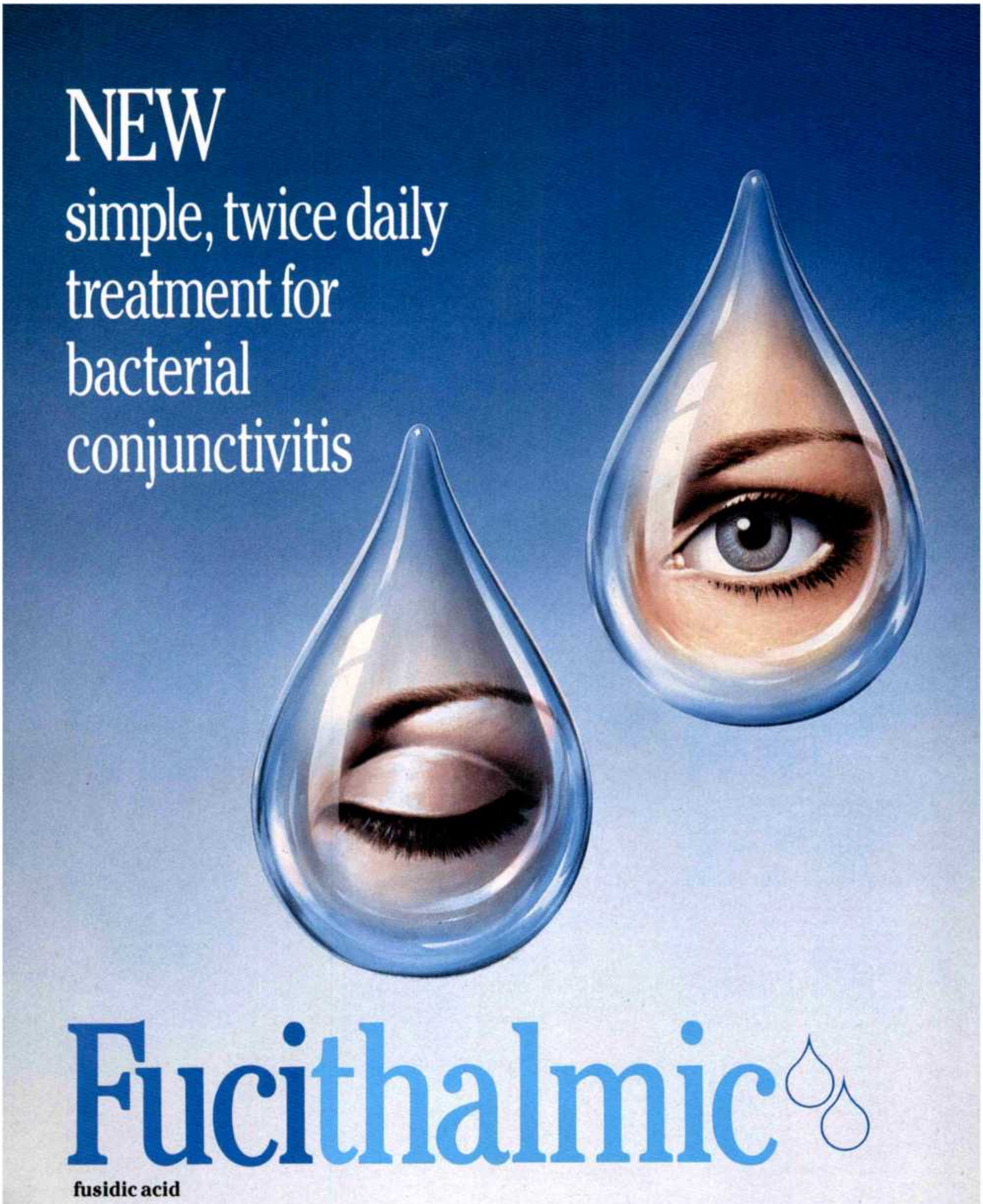
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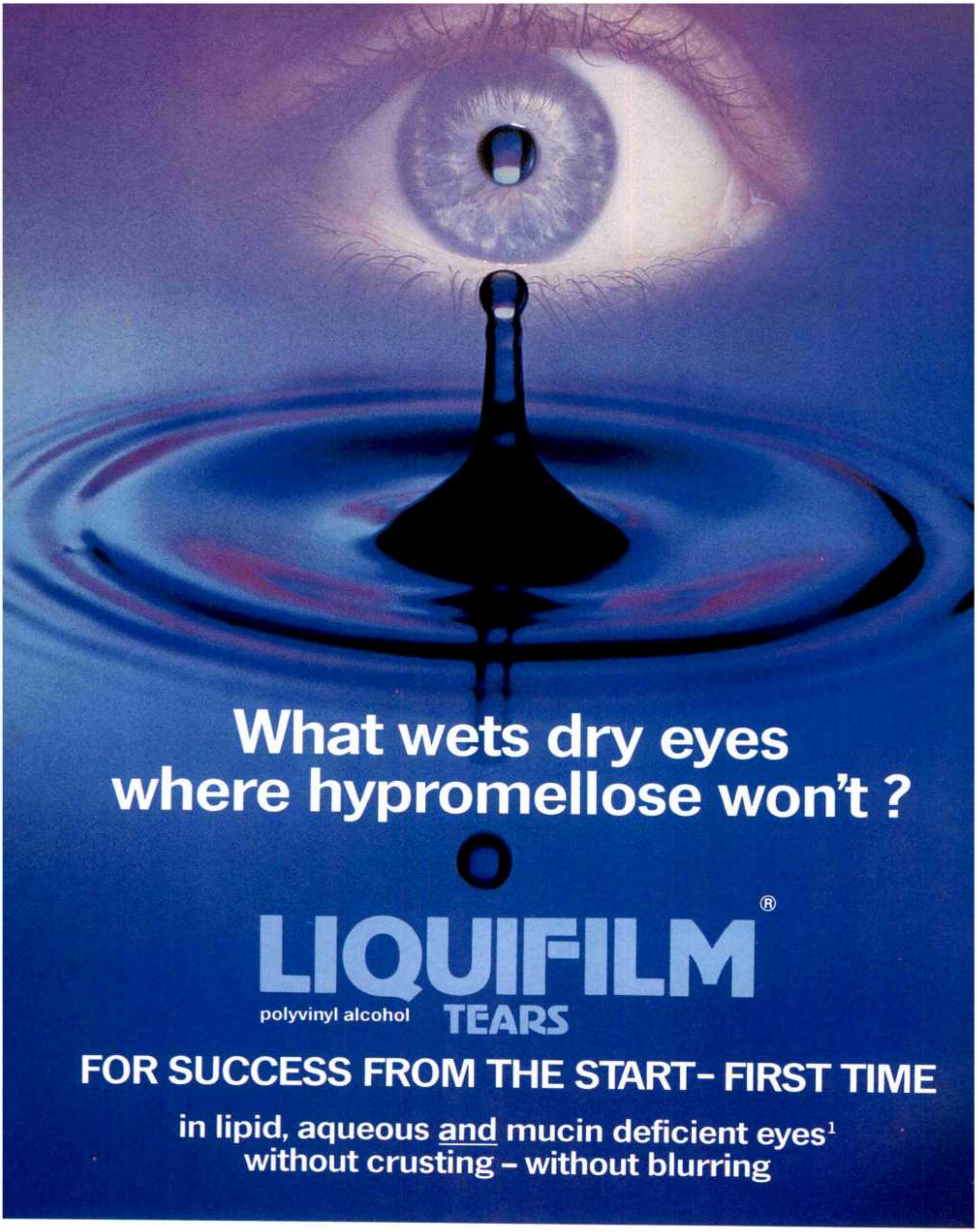
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British Journal of Ophthalmology, 1988, **72**, 737–740

Visual recovery in orbital vasculitis

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SUMMARY A 46-year-old woman with polyarteritis nodosa and chronic renal failure developed sudden loss of vision which was associated with orbital vasculitis. Treatment with cyclophosphamide produced rapid improvement in vision, which has been preserved with maintenance doses of cyclophosphamide and prednisolone.

Polyarteritis nodosa is a well recognised cause of orbital vasculitis which may be associated with visual loss due to either optic nerve compression or ischaemic optic neuropathy.[1-3] Corticosteroids, orbital irradiation,[4] and cyclophosphamide have been given as treatment, but, while the disease process and further visual deterioration may be arrested, visual recovery is rare. We report the case of a patient suffering from sudden loss of vision caused by orbital vasculitis due to polyarteritis nodosa, which responded successfully to treatment with cyclophosphamide.

Case report

A 46-year-old woman was referred to the eye clinic at the Royal Victoria Hospital, Belfast, in January 1983 for investigation of bilateral painless proptosis. The visual acuity was 6/6 in both eyes. The proptosis measured 17 mm right and 18 mm left. Both optic discs were swollen, with increased tortuosity of the retinal veins.

The patient did not return to the eye clinic for review, but in June 1983 she attended another hospital, where she was found to have chronic renal failure (serum urea 21 mmol/l and a creatine clearance of 15 ml per minute). A renal biopsy showed fibrous crescents in Bowman's capsule, with compression and hyalinisation of glomerular tufts, some of which were hypercellular. One glomerulus showed segmental necrosis. Immunofluorescence testing was positive for CIq, IgM, and fibrin. A diagnosis of polyarteritis nodosa was made following serological and clinical exclusion of systemic lupus erythematosis and subacute bacterial endocarditis. The patient was treated initially with prednisolone 40 mg daily, which was reduced later to a maintenance dose of 12·5 mg daily.

The patient returned to the eye clinic in October 1985 complaining of sudden loss of vision. The visual acuity was 6/9 in both eyes. The intraocular pressures were 22 mmHg right and 24 mmHg left Both optic discs were swollen, and fluorescein angiography showed distinct central retinal stasis, with venous return still not complete 10 seconds after filling of the retinal arterioles. The proptosis measured 20 mm right and 21 mm left. Both visual fields showed inferior altitudinal defects (Fig. 1). Both eyes showed a mixed red-green defect with the Farnsworth-Munsell 100-hue test. The pattern visually evoked response (VER) latency was delayed from both eyes, which measured 150 ms right and 130 ms left (normal range 90-120 ms). Computer assisted tomography of the orbits showed abnormal soft tissue masses behind both globes (Fig. 2). A biopsy specimen was obtained from the left orbit through a transconjunctival incision over the left medial rectus muscle. Firm rubbery tissue was felt medial to the lower border of the medial rectus, and a small wedge of tissue was excised The biopsy showed an acute vasculitis and fibrosis of orbital fat (Fig. 3) The inflammation and

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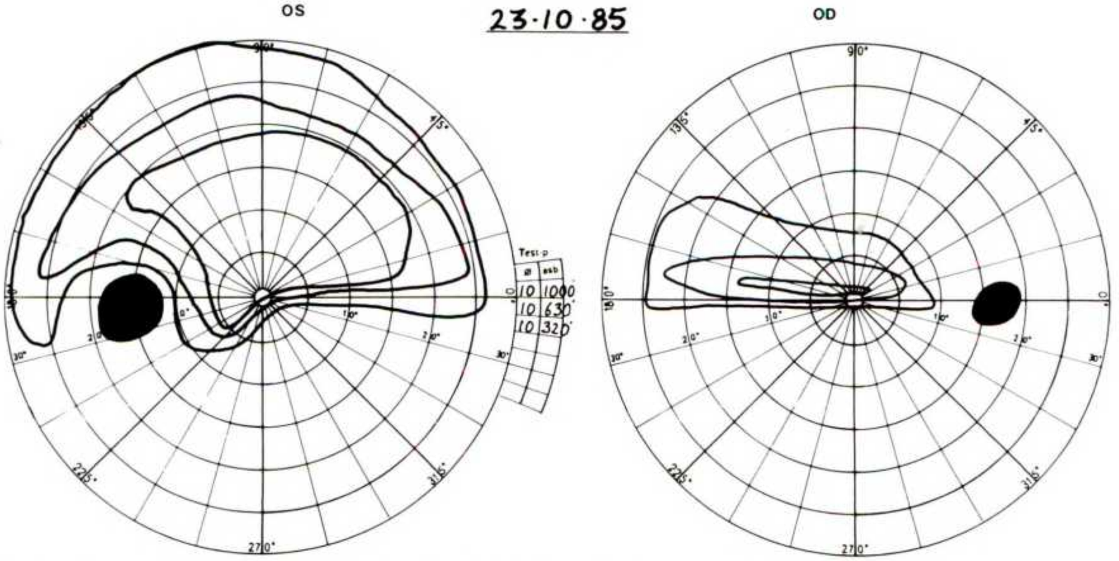

Fig. 1 *Both visual fields showed inferior altitudinal defects in October 1985.*

destruction of the blood vessel walls were consistent with polyarteritis nodosa, though in the small biopsy specimen available the vasculitis had destroyed the features which allow identification of artery from vein.

The patient was initially treated with prednisolone 40 mg daily and subcutaneous heparin injections of 5000 units twice daily. Vision deteriorated rapidly in December 1985, when visual acuity was 1/60 right eye and 6/60 left eye. In view of the rapidly failing vision the patient was treated with cyclophosphamide 200 mg daily and continued on prednisolone 40 mg daily. The visual acuity rapidly improved and in January 1986 measured 6/9 right and 6/12 left. Fluorescein angiography showed a normal circulation time at the optic discs, and late phase angiograms showed widespread choroidal folds involving the entire macular region. Both optic discs were slightly swollen. The patient was maintained on cyclophosphamide 200 mg three days a week and prednisolone 20 mg daily. In March 1987 visual acuity was 6/6 in both eyes. The visual fields showed recovery of the inferior altitudinal defects (Fig. 4), and both optic discs were pale. The patient remains on a maintenance therapy, consisting of cyclophosphamide 75 mg three days a week and prednisolone 20 mg daily.

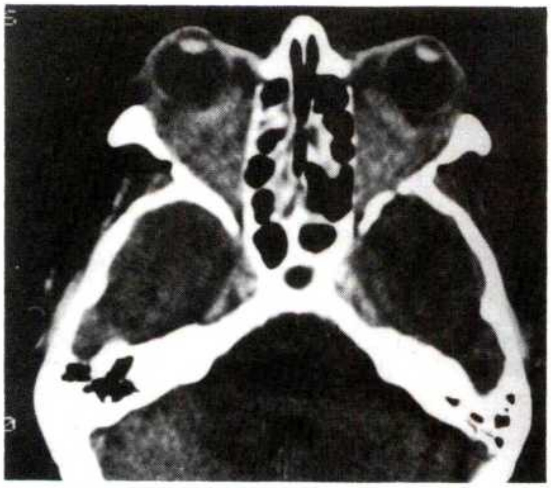

Fig. 2 *Computer tomographic scan of orbits showing abnormal soft tissue behind both globes.*

Discussion

Orbital vasculitis may be the presenting feature of polyarteritis nodosa.[5 6] We describe a patient who presented with bilateral proptosis and within a few months developed renal failure due to polyarteritis nodosa which was confirmed by renal biopsy. She retained normal vision for two years before vision deteriorated rapidly following an increase in the proptosis and consequent retinal vascular stasis. Orbital biopsy revealed an acute vasculitis and diffuse orbital fibrosis which was compatible with type 1 orbital pseudotumour described by Henderson and Farrow.[7] The visual loss was thought to be due to activation of the vasculitis with resulting optic

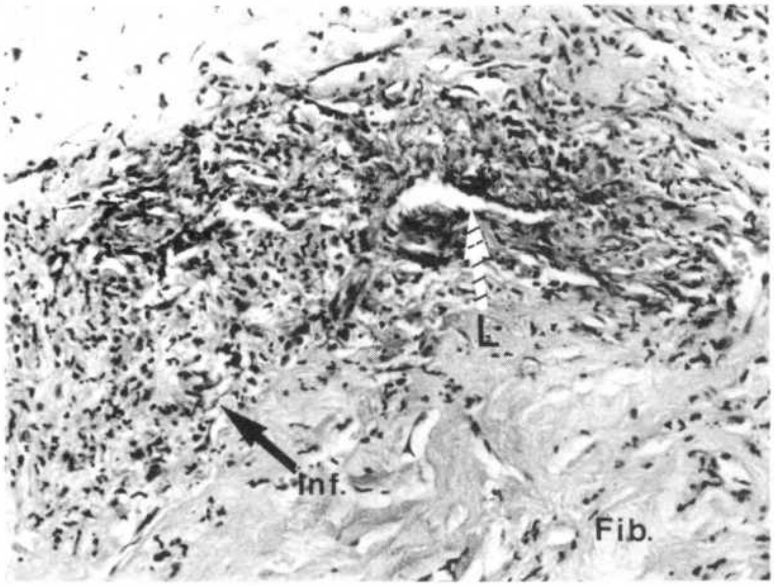

Fig. 3 *Histological section of orbital biopsy showing the lumen* (L) *of a blood vessel involved in an acute vasculitis process* (Inf). *Note the fibrosis* (Fig) *of the surrounding tissue. Haemoloxylin and eosin* ×195.

nerve compression[8] and ischaemic optic neuropathy.[3] Garrity[9] *et al.* reported on three patients with visual loss due to orbital vasculitis resistant to high-dose corticosteroids. They found cyclophosphamide to be effective in controlling the orbital pain and swelling, but visual loss was permanent. The rationale for using cyclophosphamide is its immunosuppressive effect, which is directed mainly against B cells.[10] Orbital vasculitis and polyarteritis nodosa are mediated by deposition of immune complexes in the vessel wall and are considered to be B-cell-mediated diseases.[11] One patient showed a rapid improvement of vision once cyclophosphamide was introduced, and recovery has been maintained for 18 months with a maintenance dose of cyclophosphamide and corticosteroids.

Clinicians faced with the problem of orbital pseudotumour associated with visual loss should first

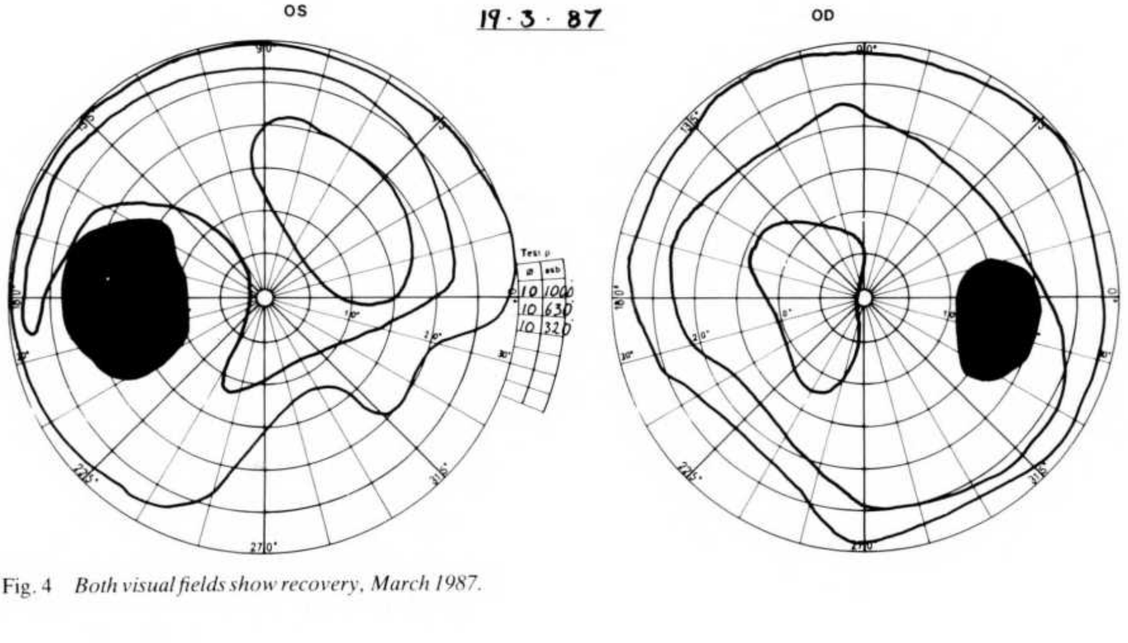

Fig. 4 *Both visual fields show recovery, March 1987.*

obtain an orbital biopsy for diagnosis and classification into either a type I vasculitis or type II lymphocytic inflammatory pseudotumour response as defined by Henderson and Farrow.[7] In cases with type I vasculitis and visual loss prompt immunosuppression of the B lymphocyte response with cyclophosphamide should should be considered as a potentially valuable method of treatment.

However, steroids and cyclophosphamide, both as short and long term drugs, have many side effects. Those of cyclophosphamide include opportunist infection, alopecia, gonadal atrophy, and haemorrhagic cystitis. These are in general reversible, but a more serious long term threat is malignancy, notably leukaemia, lymphoma, and bladder cancer.[12] Clearly long term cyclophosphamide therapy requires frequent re-evaluation. One should always be looking for an opportunity to withdraw the drug permanently or temporarily.

The authors thank Mr W C Logan, who performed the orbital biopsy, and Mrs Rosemary Hepburn, who kindly typed the manuscript

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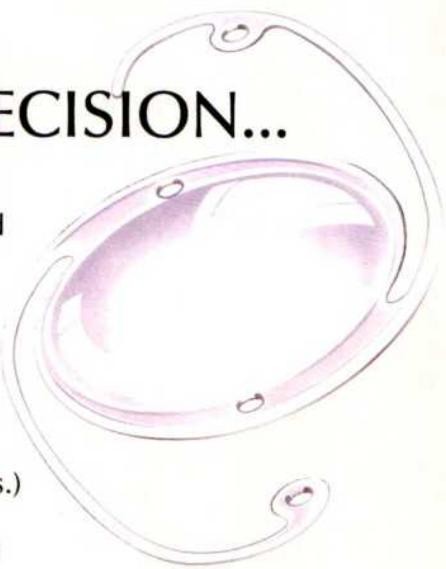

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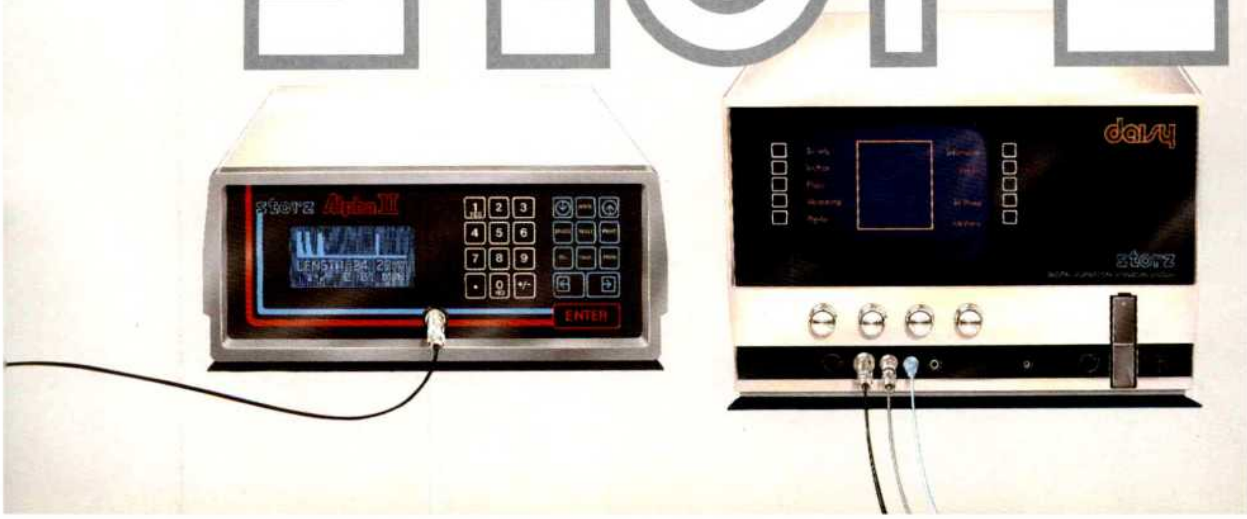

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British Journal of Ophthalmology, 1988, 72, 741–745

Effect of intraocular lens implantation on combined extracapsular cataract extraction with trabeculectomy: a comparative study

R NEUMANN, M ZALISH, AND M OLIVER

From the Department of Ophthalmology, Kaplan Hospital, Rehovot, and the Hebrew University-Hadassah Medical School, Jerusalem, Israel

SUMMARY In an attempt to assess the effect of posterior chamber intraocular lens (IOL) implantation on the outcome of combined extracapsular cataract extraction (ECCE) and trabeculectomy we compared 23 eyes subjected to ECCE and trabeculectomy with 23 eyes subjected to a triple procedure – that is, with the addition of IOL implantation. The results showed that IOL implantation did not have a detrimental effect on postoperative IOP reduction, gain in visual acuity, or needs for antiglaucoma medication. The incidence of anterior chamber reactions consisting of the development of posterior synechiae and fibrin formation was significantly higher when IOL had been implanted. However, the fibrin was generally absorbed within 14 days and the posterior synechiae did not occlude the visual axis. We conclude that IOL implantation should be included in these combined operations with the object of rehabilitating visual function.

Combined surgery for cataract and glaucoma has been performed with increasing frequency over the past decade. As the geriatric population increases, there is a growing number of candidates for this type of surgery. Another factor is the high success rate reported for procedures combining cataract extraction and trabeculectomy. Once the intracapsular method of cataract extraction had been widely replaced by the extracapsular technique, it seemed that the logical next step was to introduce a posterior chamber intraocular lens (IOL) at the same time with the object of rehabilitating phakic vision. Successful results of these triple procedures have been reported elsewhere.[1 2] However, so far as we are aware there are not yet any comparative studies assessing the advantages and disadvantages of including IOL implantation in operations combining extracapsular cataract extraction (ECCE) and trabeculectomy.

In the present study we compare a series of 23 eyes subjected to ECCE and trabeculectomy in combination with IOL implantation with a series of 23 eyes subjected to ECCE and trabeculectomy only The effects of including IOL implantation were assessed by comparing improvement in visual acuity, intraocular pressure (IOP) reduction, and immediate as well as later postoperative complications in the two series.

Materials and methods

The combined procedure of cataract extraction and trabeculectomy has been performed in our department since 1976. Early in 1985 we began to carry out triple procedures – that is, IOL implantation in addition to ECCE and trabeculectomy – and we have since included IOL implantation in all such operations except where specifically contraindicated, for example, in patients with high myopia, advanced proliferative diabetic retinopathy, or uveitis.

Two groups, each consisting of 23 patients, were studied. Each patient in the first group had undergone a combined procedure of ECCE and trabeculectomy, while those in the second group had undergone the triple procedure – that is, with the addition of IOL implantation Each group comprised the last 23 consecutive cases to have undergone either the double or the triple procedure at the time of study; patients with high myopia, proliferative diabetic retinopathy, or uveitis were excluded.

The mean postoperative improvement in visual

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acuity and reduction in IOP were compared in the two groups. In each patient improvement in visual acuity was measured in terms of the difference in the number of lines on the Snellen chart read before and after the operation. If the preoperative visual acuity was poorer than 6/120, one unit was added to the result, so that an improvement in visual acuity was indicated by a higher score. Each patient was examined with optical correction after refraction.

The mean preoperative IOP in each case was taken as the mean value obtained from the patient's last diurnal pressure curve recorded preoperatively. If no such curve had been recorded for more than three months prior to surgery, the average value of the four last consecutive IOP measurements prior to the operation was used. The mean postoperative IOP corresponded either to the mean of a diurnal pressure curve measured after surgery or, where this was unavailable, to the average value of the last four postoperative IOP measurements recorded in the patient's file. The postoperative reduction in IOP was obtained by simple subtraction.

The amount of antiglaucoma medication before and after surgery was compared in the two groups. Also compared were the incidence of immediate and later surgical complications, including anterior chamber reactions, anterior chamber depth, and formation of posterior synechiae.

The mean period of follow-up was 10·9 months (range 5–18 months) in patients who underwent the combined procedure of ECCE and trabeculectomy, and 3·8 months (range 2–10 months) in those who underwent the triple procedure.

PROCEDURES

Cataract extraction was performed under local or general anaesthesia, depending on our prior assessment of the patient's ability to comply with the instructions of the surgical team during the operation. Local anaesthesia was used whenever possible. Following peritomy of 160–180° and conjunctival reflection, a 3×3 mm limbus-based scleral flap was cut to the desired depth and usually at the 12.00 o'clock position. A corneoscleral groove over 160–180°C and two preplaced sutures were prepared on both sides of the scleral flap. A small opening was then made in the anterior chamber, usually close to the scleral flap, and anterior capsulotomy was carried out by the can-opening technique. A corneoscleral incision was made along the groove, and directed slightly towards the cornea at the site of the scleral flap. The lens nucleus was expressed and the preplaced sutures were then tied with a slip or final knot, depending on whether IOL implantation was planned or not. The lens cortex was aspirated by a Kelman aspirator or a McIntyre syringe. In patients receiving an IOL the temporary slip knots were opened and the IOL was implanted in the posterior chamber. An intraocular lens of the modified J loop type was used in each case. The corneoscleral incision was closed, first temporally and then nasally, by means of 10–0 Ethilon sutures.

Following wound closure on both sides of the scleral flap a piece of tissue from the trabeculum area (2×2·5 mm) was resected, iridectomy was performed at the site of the trabeculectomy, and the scleral flap was sutured with 4 or 6 separate 10–0 nylon sutures. In eyes in which the anterior chamber was found to be shallow the irrigation aspiration procedure was followed by the injection of sodium hyaluronate (Healonid) in order to reform the anterior chamber. At the completion of the operation the anterior chamber was always well formed. The conjunctival flap was placed back in position and sutured with two single 9·0 braid silk sutures.

Results

Table 1 presents the clinical characteristic of the two groups studies, namely, the 23 patients who underwent the triple procedure of ECCE, trabeculectomy, and IOL (group A) and the 23 who underwent ECCE

Table 1 *Clinical findings*

Surgical procedure	*No of eyes*	*Mean age (yr)*	*Male/ female*	*Open angle glaucoma Primary*	*Secondary*		*Angle closure glaucoma*	*Mean follow-up (months)*
				Simple	*Pseudo-exfoliation*	*Pigmentary*		
Group A ECCE+IOL+trabeculectomy	23	72·7 (61–83)	10/13	10	4	2	7	3 8
Group B ECCE+trabeculectomy	23	73 9 (58–86)	12/11	6	10	—	7	10 9

Table 2 *Mean visual acuity improvement and mean IOP reduction after surgery*

Surgical procedure	*Mean improvement in visual acuity (units)*	*Mean pressure reduction (mmHg)*
Group A ECCE+IOL+ trabeculectomy	3·13±0·49	6·27±0·97
Group B ECCE+trabeculectomy	3·74±0·62	6·47±1·25

and trabeculectomy only (group B). The mean ages in the two groups were similar and there were no significant sex differences between them. Sixteen patients in each group suffered from open angle glaucoma (primary and secondary). The numbers of patients with angle closure glaucoma, pseudoexfoliation glaucoma, and pigmentary glaucoma are indicated in the table.

A comparison of the operative results in terms of mean improvement in visual acuity and mean reduction in IOP shows no differences between the two groups (Table 2).

Table 3 summarises the incidence of postoperative complications. Anterior chamber reaction was significantly higher in patients of group A, where 11 eyes showed fibrin formation on the surface of the lens and iris as compared with only five in group B. The fibrin was readily absorbed within 14 days following local steroid treatment. Thirteen eyes of group A developed posterior synechiae and iris retraction, leading to anterior positioning of the lens in front of the iris, usually sectorial. Posterior synechiae developed in only seven eyes of group B, and they did not occlude the visual axis in either group. Shallow anterior chamber was observed in about one-quarter of the patients in each group, usually on the first or second day after surgery, but deepened within seven days in each case.

Table 3 *Number of eyes with postoperative complications*

Surgical procedure	*Fibrin*	*Shallow chamber*	*Iris retraction**
Group A ECCE+IOL+ trabeculectomy	11	6	13
Group B ECCE+ trabeculectomy	5	5	7

*This refers to positioning of the iris behind the IOL, usually sectorial

Table 4 shows the number of eyes receiving various types of antiglaucoma medication before and after surgery. It can be seen that surgery was followed by a substantial drop in the number of patients requiring such medication, with no significant differences between the groups. It should be noted that four patients from group A were excluded from this assessment because they continued to receive full treatment for reasons not relevant to the operation outcome: two of them did not understand our instructions to stop taking medication, while two were instructed to continue with medication because of high pressure in the fellow eye.

Discussion

Both glaucoma and cataract are most often found in geriatric populations A considerable proportion of glaucomatous patients show cataractous changes as well, usually – but not always – of the nuclear sclerotic type.

We consider three groups of patients with cataract and glaucoma as candidates for combined surgery.

Firstly, those in whom glaucoma cannot be controlled despite maximum tolerable medication, and in whom a cataract severely impairs vision. Combined surgery is clearly indicated in such cases

Secondly, those in whom cataract extraction is clearly indicated and in whom glaucoma is controlled

Table 4 *Number of eyes receiving pre- and postoperative antiglaucomatous medication*

	*Acetazolamide+ eye drops**		*Eye drops only**		*Eye drops one drug regiment†*		*Free from treatment*		*Total no of eyes*
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	
Group A ‡ECCE+IOL+ trabeculectomy	15	3	7	1	0	5	0	10	19
Group B ECCE+trabeculectomy	12	3	7	1	4	5	0	14	23

*Pilocarpine 2% adrenaline 1% (Eppy), and timolol ½% in various combinations

†Either pilocarpine or timolol

‡Not included here among the patients receiving postoperative medication are two patients who continued to take medication through misunderstanding instructions and two who continued to take acetazolamide because of uncontrolled IOP in the fellow eye.

by intensive therapy including carbonic anhydrase inhibitors. While surgical intervention for glaucoma would not normally be recommended for these patients, the fact that they must be operated on for cataract raises the possibility of adding a filtration procedure at the same time. A number of advantages are to be gained from this. (1) Antiglaucoma medication can then be reduced, thus improving compliance on the part of the patient. (2) A filtration procedure as an adjunct to cataract extraction may avert the IOP increase which is known to follow cataract surgery in the early postoperative days.[3] This increase is especially hazardous for severely damaged optic discs. (3) The possible need for a second operation is avoided. Reoperation, in addition to imposing stress on elderly and infirm patients has certain specific drawbacks. For example, the lens must be removed through a corneal incision or at a section of the limbus at a distance from a future possible trabeculectomy site. It is our experience that these operations are less successful than with the regular method. We are impressed that these patients in whom glaucoma is controlled with intensive medication tend to have a raised IOP and to experience loss of glaucoma control in time. We therefore tend to favour combined surgery for these patients.

Thirdly, those in whom glaucoma surgery is indicated because maximum tolerable therapy does not control IOP levels, and a developing cataract has already caused partial impairment of the visual acuity Although cataract extraction would not normally be recommended at this stage, the proposed filtering surgery for the glaucoma is likely to aggravate the cataractous changes in these patients. Reoperation for cataract after a filtering operation may inadvertently cicatrise a well-formed filtration bleb even when the cataract is removed through a corneal incision. Moreover, having the cataract removed allows improved follow-up and monitoring of the glaucoma by examination of the optic disc and visual field unhampered by opaque media We would therefore advocate the combined procedure for this group of patients as well. It should be noted that IOL implantation is strongly recommended in this group of patients because their visual acuity prior to surgery is fairly good. Failure to implant an IOL would seriously hamper the rehabilitation of their visual function.

The purpose of this study was to clarify whether the outcome of the combined operation might be detrimentally affected by the addition of a third procedure, namely IOL implantation for restoration of phakic vision. Satisfactory results have been reported for the combined procedure without IOL implantation.[4] In our study the inclusion of an IOL in the procedure was evaluated in terms of the following criteria: (*a*) improvement of VA; (*b*) reduction of IOP; (*c*) anterior segment complications; (*d*) reduction of medication after surgery.

We therefore compared a group of 23 eyes that underwent the triple procedure with a similar group that underwent only ECCE and trabeculectomy. About half of the patients in each group were poor candidates for visual acuity improvement, mainly because of age related macular degeneration (ARMD) and severely damaged optic disc. This may explain the rather modest levels of mean improvement in visual acuity found in both groups (3·5 lines of the Snellen chart). It should be pointed out that, whenever the posterior segment was healthy, the visual acuity improvement was up to 7 lines on the Snellen chart. Despite the lack of difference between the groups with regard to visual acuity improvement, there is unanimous agreement that the restoration of phakic vision through IOL implantation is of great advantage to the patient.

The degree of IOP reduction was almost the same in the two groups (Table 2). These values become more meaningful when examined in the light of pre- and postoperative medical therapy. As Table 4 shows, 14 patients who did not receive IOL and 10 patients who did were relieved of all antiglaucoma medication after surgery. Only three patients in each group continued to require treatment with carbonic anhydrase inhibitors.

Eleven patients in whom the IOP was controlled before operation were nevertheless operated on for other reasons such as their poor tolerance to antiglaucoma therapy. None of them required heavy medication after surgery.

The number of patients suffering postoperative anterior chamber reactions differed in the two groups. Eleven of the eyes with IOL implants and five without implants developed fibrin in the anterior chamber within a few days after surgery. In all of them the fibrin was completely absorbed within about two weeks. More than half (13/23) of the eyes with IOL and only seven eyes without it developed iris retraction with posterior synechiae. Since the iris retraction did not block the visual axis in any of these eyes, it did not reduce the final visual acuity.

These results show that in both groups there was a relatively high degree of postsurgical reactions in the anterior chamber. It should be remembered that these patients had been treated for long periods of time, most of them for years, with pilocarpine and other drugs for glaucoma. It is a common experience that prolonged periods of treatment with miotic drugs render the iris atrophic and prone to the formation of posterior synechiae. Thus, anterior segment surgery in those patients is often accompanied by pupillary distortion. Pupillary irregularity is also due to the unresponsiveness of the iris musculature to the commonly used midriatic solutions during and after surgery. The presence of a foreign body such as an IOL in these eyes probably enhances the reactions mentioned above to a still higher degree This explains the higher percentage of fibrinous exudate, iris retraction, and posterior synechiae found in the pseudophakic patients (Table 3). No significant difference was found in the postoperative shallowing period of the anterior chamber between the groups. We therefore do not consider this condition to be a cause of the pupillary distortions finally resulting.

A shallow anterior chamber was observed in the immediate postoperative period in six eyes with and five without an IOL, lasting for not more than one week. In no case was the anterior chamber flattened completely.

Other authors have reported that posterior chamber implantation of IOL concomitantly with ECCE in glaucomatous eyes has no effect on the incidence of postoperative IOP elevation.[3] This is in agreement with our present findings that the inclusion of IOL implantation in the combined procedure of ECCE and trabeculectomy did not adversely affect the average reduction in IOP. There was also no detrimental effect on the postoperative medication regimen or the visual acuity improvement.

It is well known that IOL implantation offers the best chance of restoring vision, even in patients with ARMD or glaucomatous optic nerve damage. Postoperative complications, although more common with IOL implantation, did not affect the final results. We therefore conclude that combined surgery for glaucoma and cataract should not normally be considered a contraindication for IOL implantation unless there are other specific contraindications, such as uveitis, high myopia, or advanced proliferative diabetic retinopathy.

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The consensual ophthalmotonic reaction

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SUMMARY The consensual ophthalmotonic reaction describes the phenomenon whereby alteration of the intraocular pressure in one eye is accompanied by a corresponding pressure change in the contralateral eye. Thirteen normal and thirteen ocular hypertensive subjects received 0·5% timolol, 2% pilocarpine, 1% adrenaline, or saline uniocularly with saline to the other eye under double blind, randomised conditions. Intraocular pressure was measured by applanation tonometry at 0, 30, 60, 120, and 240 minutes. Falls in pressure were found in both treated and consensual eyes for all treatments in both subject groups. A linear relationship between the fall in pressure in the treated eye and that in the consensual eye was found for timolol and pilocarpine but not for adrenaline.

In 1924 Weekers[1] coined the phrase 'consensual ophthalmotonic reaction' to describe the phenomenon whereby alteration of the intraocular pressure (IOP) in one eye is accompanied by a corresponding pressure change in the contralateral eye. This response was reported initially in animals, where uniocular fistulisation operations,[2] anterior chamber collapse,[3] aqueous expression,[4] and various antiglaucoma medications[5-7] were found to lower IOP in the consensual eye. Similarly, manoeuvres designed to increase the IOP in one eye, such as topical nitrogen mustard,[8] stimulation of the fifth cranial nerve,[9] and intracameral injection of prostaglandins[10] were found to raise the consensual IOP in some cases.

In man a consensual response to timolol has been convincingly shown in normal and glaucomatous subjects, both in single doses and in prolonged treatment studies.[11-13] Sporadic reports have also cited consensual pressure falls in response to uniocular adrenaline[14] and pilocarpine[15] and following uniocular tonography[16] and 360° laser trabeculoplasty.[17]

The objectives of the present study were (1) to confirm the existence of the consensual ophthalmotonic reaction in man; and (2) to elucidate the aetiology of the consensual ophthalmotonic reaction by determining whether or not a consensual pressure response occurred regardless of the nature of the drug used to lower the pressure in the treated eye, and if so, whether the consensual response bore a direct relationship to the effect of the drug in the treated eye.

Subjects and methods

SUBJECTS

Group A consisted of 13 healthy male volunteers aged 28 to 63 years (mean age 44 years) with normal corrected visual acuity, results of slit-lamp and ophthalmoscopic examination, IOP between 10 and 19 mmHg, full visual fields on Bjerrum screen testing, and normal optic discs. They were not taking any medication.

Group B consisted of 13 ocular hypertensive volunteers, 11 male and two female, aged 43 to 82 years (mean 63 years) with an IOP >21 mmHg in one or both eyes on three or more occasions, without glaucomatous visual field loss or optic disc cupping, and with open drainage angles.

METHODS

Every subject attended at the same time of day on four occasions, each separated by at least one week. On each visit one drop of one of the following – 0·5% timolol, 1% adrenaline, 2% pilocarpine, or saline—was administered uniocularly, with saline given to the other eye. The eye treated and the treatment order were randomly selected and the drugs applied under double blind conditions.

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IOP measurements were made before and at 30, 60, 120, and 240 minutes after drug administration. Measurements were made in both eyes (right eye first on each occasion) by applanation tonometry under topical 0·4% benoxinate anaesthesia. Three measurements were taken for each reading and averaged.

STATISTICAL METHODS

Repeatability was assessed by calculating the within-individual coefficient of variation for starting intraocular pressures within occasions and between occasions.

The IOP changes as a function of time were calculated for the treated and consensual eyes as the area under the curve in mmHg.min by means of the trapezoid rule. 'The integrated drug effect' (IDE) was calculated by subtracting the values obtained for the saline experiments from those of the drug experiments in order to exclude any effect that repeated tonometry or diurnal variation might have had on the IOP.

To determine the relation between drug effects on the treated and consensual eyes, regressions of IDE in the consensual eyes on IDE in the treated eyes for all subjects and treatments were calculated. The significance of differences between subjects and treatments was assessed by analysis of covariance by standard methods.

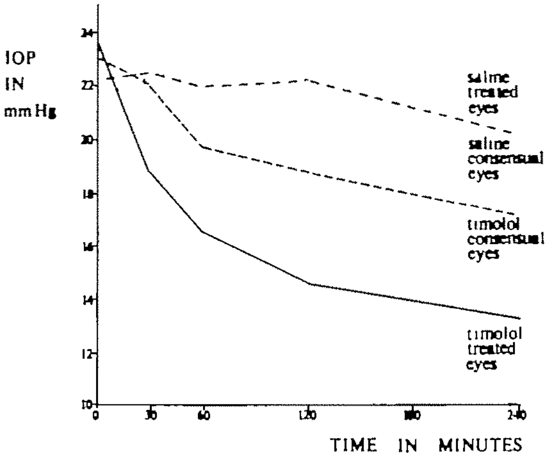

Fig. 1 *Mean intraocular pressure in mmHg versus time in minutes after treatment in 13 ocular hypertensive subjects: in the timolol 0·5% treated eyes (___) and their consensual eyes (____), and in the saline treated eyes (....) and their consensual eyes (_ _).*

Results

0·5% Uniocular timolol administration produced a fall in IOP in both treated and consensual eyes in both subject groups. The effect of timolol as opposed to saline on the IOP in the ocular hypertensive group is shown in Fig. 1. The starting pressures and maximum pressure reductions for each group and each treatment are shown in Table 1. The IDE for both eyes of each subject group with each treatment used is shown in Table 2.

GROUP A

In the normotensive group the starting IOP was 13·9±0·1 mmHg (mean±SEM). The coefficient of variation for starting IOP within occasions was 4·3% and between occasions was 8·9%.

Timolol produced a maximum fall in IOP in the treated eye of 5·2±0·3 mmHg and in the consensual eye of 2·6±0·3 mmHg. This resulted in a significant IDE in both the treated eye (p<0·0005) and the contralateral eye (p<0·025).

Adrenaline produced a maximum fall in IOP in the

Table 1 *Mean starting IOP±SEM and maximum fall in IOP±SEM in mmHg for treated and consensual eyes for each treatment and each subject group*

	Normotensives		*Ocular hypertensives*	
	Starting IOP	*Maximum fall in IOP*	*Starting IOP*	*Maximum fall in IOP*
Treated eyes				
Timolol	14·1±0·4	5·2±0·3	23·8±0·8	10·9±0·7
Adrenaline	14·5±0·5	3·7±0·3	23·8±0·5	6·8±0·5
Pilocarpine	13·7±0·3	3·4±0·2	22·6±0·6	5·6±0·5
Saline	13·5±0·3	1·2±0·3	21·7±0·5	2·2±0·4
Consensual eyes				
Timolol	13·8±0·4	2·6±0·3	22·9±0·6	5·9±0·5
Adrenaline	14·0±0·4	2·2±0·2	22·8±0·5	3·7±0·3
Pilocarpine	14·0±0·3	2·3±0·2	22·0±0·5	3·0±0·4
Saline	13·7±0·3	1·4±0·3	22·3±0·4	2·1±0·4

Table 2 *Mean integrated drug effect in mmHg min ±SEM for treated and consensual eyes for each treatment and each subject group.*

	Normotensives	*Ocular hypertensives*	*All subjects*
Treated eyes			
Timolol	14·06±2·09***	33·48±4·16***	23·77±2·99***
Adrenaline	6·00±1·77**	13·35±3·72**	9·67±2·15***
Pilocarpine	5·64±1·42**	10·76±2·50***	8·20±1·50***
All treatments	8·57±1·18***	19·20±2·58***	13·88±1·53***
Consensual eyes			
Timolol	4·16±1·66*	12·92±3·55**	8·54±2·11***
Adrenaline	−0·05±4·19 NS	4·27±2·18*	3·65±1·49**
Pilocarpine	1·63±2·18 NS	5·98±2·19**	3·80±1·58**
All treatments	2·94±1·14**	7·72±1·64***	5·33±1·03***

*=p<0·05, **=p<0·0125, ***=p<0·001

treated eye of 3·7±0·3 mmHg and in the consensual eye of 2·2±0·2 mmHg. This resulted in a significant IDE in the treated eye (p<0·0025) but not in the consensual eye.

Pilocarpine produced a maximum fall in IOP in the treated eye of 3.4±0·2 mmHg and in the consensual eye of 2·3±0·2 mmHg. This resulted in a significant IDE in the treated eye (p<0·0025) and a consensual response that did not reach statistical significance.

When all treatments were considered together, the IDEs in both the treated and consensual eyes were statistically significant (p<0·0005 and p<0·01, respectively).

GROUP B

In the ocular hypertensive group the starting IOP was 22·7±0·2 mmHg. The coefficient of variation for the starting IOPs within occasions was 3·4% and between occasions was 9·6%.

Timolol produced a maximum fall in IOP in the treated eye of 10·9±0·7 mmHg and in the consensual eye of 5·9±0·5 mmHg. This resulted in a significant IDE in both the treated eye (p<0·0005) and the consensual eye (p<0·0025).

Adrenaline produced a maximum fall in IOP in the treated eye of 6·8<0·5 mmHg and in the consensual eye of 3·7±0·3 mmHg. This resulted in a significant IDE in the treated eye (p<0·0025) and in the consensual eye (p<0·05).

Pilocarpine produced a fall in IOP in the treated eye of 5·6±0·5 mmHg and in the consensual eye of 3·0±0·4 mmHg. This resulted in a significant IDE in both treated and consensual eyes (p<0·005 and p<0·01, respectively).

When all treatments were considered together, the IDEs in both treated and consensual eyes were highly statistically significant at p<0·0005.

Table 3 *Relationship between the integrated drug effect in the treated eye and that in the consensual eye for all subjects for each treatment and the analysis of covariance for this relationship*

	Slope	*r*	*p*
Timolol	0·48	0·678	<0·001
Adrenaline	0·09	0·135	NS
Pilocarpine	0·59	0·565	<0·01
All treatments	0·37	0·545	<0·001
Analysis of covariance		*F*	*p*
Between treatments		3·241	<0·05
Between subjects		0·768	NS
Comparison of slopes between subject groups		0·253	NS
Comparison of elevations between subject groups		0·096	NS

COMBINED SUBJECT GROUPS

When both subject groups were considered together, timolol was seen to produce highly significant IDEs in both treated and consensual eyes at p<0·0005. Adrenaline also produced significant IDEs in both treated and consensual eyes (p<0·0005 and p<0·0125, respectively) as did pilocarpine (p<0·0005 and p<0·0125, respectively).

The graph of IDE in the consensual eyes versus IDE in the treated eyes for all subjects and treatments is shown in Fig. 2, while Table 3 shows the regression correlation and analysis of covariance.

A statistically significant correlation between IDEs in the treated and consensual eyes was found for timolol (p<0·001) and pilocarpine (p<0·01) and for all treatments when considered together (p<0·001) but not for adrenaline. Analysis of variance confirms a source of variance between treatment groups but not between subject groups.

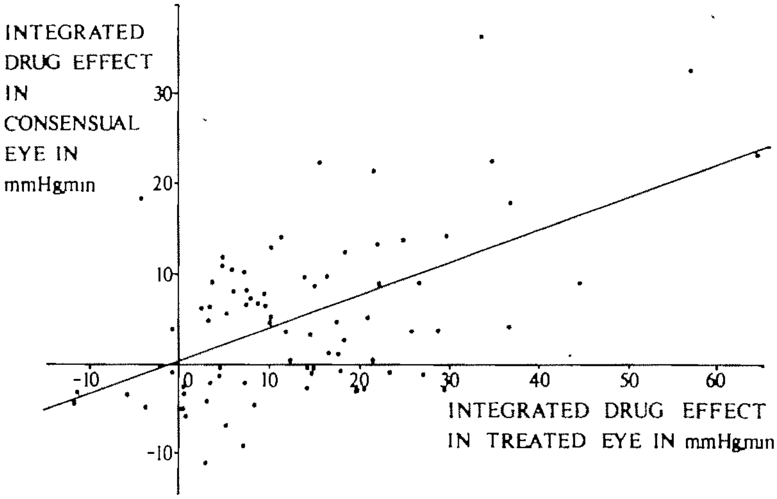

Fig 2 *Integrated drug effect in mmHg.min in the treated eye versus that in the consensual eye for all subjects and treatments. The line of best fit calculated by the method of least squares is shown.*

Discussion

In this study a consensual fall in IOP was seen to occur following uniocular administration of timolol, adrenaline, and pilocarpine in the hypertensive study group. This supports the hypothesis that the consensual ophthalmotonic reaction (COR) occurs in man regardless of the drug used to lower IOP in the treated eye. In the normotensive group, however, a significant COR was seen only with timolol.

The correlation shows that for all subjects and treatments the fall in IOP in the consensual eye is directly linearly related to that in the treated eye. It should be noted that each drug produced a smaller IDE in the treated eyes of the normotensive group than in the ocular hypertensive subject group. Since the COR is proportional to the IDE in the treated eye, this might account for the COR of the normals treated with pilocarpine and adrenaline failing to reach statistical significance. Adrenaline is unusual, however, in that it does not show a statistically significant regression correlation between treated and consensual eyes when considered alone.

Several hypotheses have been formed to try to explain the consensual ophthalmotonic reaction. One suggests that topical medication is absorbed systemically and either has its action on the fellow eye via the blood stream or acts centrally on IOP control mechanisms. The incidence of systemic side effects after topical timolol supports this theory, but studies with pindolol by Smith *et al.*[18] tend to refute it. They measured IOP falls after topical and intravenous administration of pindolol. Pindolol treatment to one eye resulted in a pressure fall in the contralateral untreated eye. This was unlikely to have resulted from systemic absorption of the drug, since the contralateral fall occurred in the presence of far lower plasma concentrations than were present after intravenous administration, which gave a comparable reduction in pressure. The theory is also unable to explain the consensual ophthalmotonic reaction seen on mechanical alteration of IOP such as following laser trabeculoplasty and tonography.

An alternative hypothesis suggests that a nervous mechanism exists whereby changes in IOP in one eye provoke a reflex alteration in pressure in the fellow eye. This was first postulated by Leplat,[19] who found that a controlled blow to a rabbit eye produced a more marked consensual response if the animal was unanaesthetised and that the response could be abolished by retrobulbar cocaine to the treated eye.

If such a nervous reflex exists it is unusual in that the reflex pressure response is in the same direction as the original pressure disturbance—a form of positive feedback which would exclude it from serving any homoeostatic purpose. The practical importance of the consensual ophthalmotonic reaction is that in studies of IOP responses to a particular treatment the fellow eye should not be used as a control.

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Sympathetic influences on the consensual ophthalmotonic reaction

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SUMMARY Six patients with intraocular hypertension received 0·5% timolol or saline uniocularly with saline to the other eye, and the intraocular pressure was measured by applanation tonometry at 0, 30, 60, 120, and 240 minutes. Falls in pressure were seen in both the timolol treated and consensual eyes. The same experiments were conducted after pretreatment of the consensual eyes with guanethidine 5%. The consensual ophthalmotonic reaction (COR) to timolol administration was blocked by pretreatment with guanethidine. Three out of four patients with Horner's syndrome also showed a reduced COR in the affected eye after timolol administration to the normal eye, suggesting that the COR is mediated by a nervous reflex with the efferent limb in the sympathetic nervous system.

The consensual ophthalmotonic reaction (COR) describes the phenomenon whereby alteration of the intraocular pressure (IOP) in one eye is accompanied by a corresponding pressure change in the contralateral eye. It has been postulated that the COR is mediated via a nervous reflex mechanism; however, the pathways involved have not been shown. Prijot and Stone,[1] using uniocular compression as their initiating stimulus, found that the COR was not observed in atropinised rabbits and concluded that the parasympathetic nervous system might be involved.

Perkins,[2] using stimulation of the fifth cranial nerve in rabbits to alter the IOP, found that the COR was diminished by profound narcosis and abolished by section of the fifth nerve on the consensual side, and he suggested that an axon reflex with the efferent limb in the fifth nerve might exist. Akagi *et al.*,[3] however, in experiments where they artificially raised the IOP in the treated eye to provoke a consensual response, found that section of the fifth nerve on the *treated* side prevented the COR; and that the COR was inhibited by blocking the cervical sympathetic on the consensual side. Akagi *et al.* therefore deduced that the sympathetic nervous system might provide the efferent limb of the reflex.

The aim of this study was to determine whether sympathetic dysfunction, whether induced by disease or drug, altered the COR in the human eye.

Subjects and methods

SUBJECTS

The study group for experiment 1 comprised six ocular hypertensive volunteers, five male and one female, aged 45 to 76, with an IOP >21 mmHg in one or both eyes on three or more occasions but without glaucomatous visual field loss or optic disc cupping and with open drainage angles.

The study group for experiment 2 consisted of four volunteers, three male and one female, aged 28 to 54 with unilateral Horner's syndrome. Each showed features of ptosis and a small pupil with a slow redilatation phase of the light reflex, as seen on pupillometric measurement, and diminished response to the topical instillation of cocaine 4%. None was receiving any ocular or systemic therapy.

METHODS

Experiment 1

Every subject attended on four occasions at the same time of day, each separated by at least one week. Prior to two of these visits pretreatment with one drop of guanethidine 5% was administered by the subject to the right eye twice daily for three days.

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Prior to the other two visits the subjects received no pretreatment. On the experimental days the subjects received either one drop of timolol 0·5% to the left eye and saline to the right eye or saline to both eyes. This drug administration was carried out under double-blind conditions according to a factorial design (see Table 1).

IOP measurements were taken before and at 30, 60, 120, 240, and 360 minutes after drug administration. Measurements were taken in both eyes (right eye first on each occasion) by applanation tonometry under topical 0·4% benoxinate anaesthesia. Three measurements were taken for each reading and averaged.

Repeatability was assessed by calculation of the coefficient of variation for the starting pressures within occasions and between occasions for the visits when no pretreatment was administered.

Experiment 2

Each of the four patients with Horner's syndrome attended on three occasions. On one occasion one drop of 0·5% timolol was instilled into the affected eye and saline to the normal eye. On another visit saline was administered to both eyes, and on a third visit timolol was instilled into the normal eye and saline to the affected eye. The treatment order was randomly selected and applied double blind.

IOP measurements were made before and at 30, 60, 120, 240, and 360 minutes after treatment.

STATISTICAL METHODS

For each series of experiments IOP changes as a function of time were calculated for the treated and consensual eyes as the area under the curve (AUC) from the time of treatment administration using the trapezoid rule. The results from the six ocular hypertensives were averaged. The 'integrated drug effect' was calculated by subtracting the values obtained for the saline experiments from those of the timolol experiments in order to exclude any effect that repeated tonometry or diurnal variation might have on IOP.

Results

EXPERIMENT 1

The mean starting IOP for the six ocular hypertensives was 21·9 mmHg. The coefficient of variation for the starting IOPs on the non-pretreatment days was 3·4% within occasions and 9·6% between occasions. The mean AUCs for each eye and each study day are shown in Table 1.

When no pretreatment was given and saline was administered to both eyes (visit D), the IOP changes with time were small, representing diurnal variation and any effect that repeated applanation might have on IOP. The calculated AUC for both eyes under these circumstances was not significantly different from zero.

When timolol was administered to the left eye in the absence of pretreatment (visit C), a fall in IOP was seen in both treated and consensual eyes. The AUCs were statistically significant for both eyes ($p<0.0025$ for the treated eyes and $p<0.025$ for the consensual eyes).

The integrated drug effect (shown in Table 1) for the timolol treated eyes was 39·0 mmHg.min and for the consensual eyes was 25·5 mmHg.min ($p<0.0025$ and $p<0.05$, respectively).

Guanethidine pretreatment lowered the starting IOP by 4·81±0·9 mmHg (mean±SEM) in the treated eye and by 1·55±0·4 mmHg in the contralateral eye. Analysis of variance showed the difference in starting

Table 1 *Mean area under curve and integrated drug effect in mmHg min (±SEM) for timolol and saline treated eyes with and without pretreatment with guanethidine*

	Visit A		*Visit B*		*Visit C*		*Visit D*	
Eye	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*	*Right*	*Left*
Pretreatment	Guaneth	Nil	Guaneth	Nil	Nil	Nil	Nil	Nil
Treatment	Saline	Timolol	Saline	Saline	Saline	Timolol	Saline	Saline
Mean AUC	11·9	25·8	10·6	1·3	21·4	36·6	−4·0	−2·4
SEM	5·4	8·3	3·9	2·2	7·3	7·8	4·5	3·2
p	<0·05	<0·0125	<0·025	NS	<0·025	<0·0025	NS	NS

	Visit A minus visit B		*Visit C minus visit D*	
Eye	*Right*	*Left*	*Right*	*Left*
Integrated drug effect	0·4	24·5	25·5	39·0
SEM	6·5	7·8	10·9	7·7
p	NS	<0·025	<0·05	<0·0025

IOP to be significant in the pretreated eye (p<0·01) but not in the contralateral eye.

When guanethidine pretreatment was given and saline administered to both eyes (visit B), a fall in IOP was seen in the pretreated eyes during the study day. The AUC for the pretreated eyes was significantly different from zero (p<0·025) but for the fellow eyes it was not.

Pretreatment of the right eyes with guanethidine followed by treatment of the left eyes with timolol (visit A) resulted in a fall in IOP in both the timolol treated and consensual eyes. The AUCs for both eyes were statistically significant (p 140·0125 for the treated eyes and p<0·05 for the consensual eyes).

AUCs from the guanethidine and saline study were subtracted from those of the guanethidine and timolol study in order to exclude the effect on IOP that guanethidine itself was seen to produce. The resulting drug effect for the timolol treated eyes was 24·5 mmHg.min (p.<0·025) and for the consensual pretreated eyes was 0·4 mmHg.min, which was not statistically significant. Thus uniocular treatment with timolol causes a fall in IOP in both the treated and consensual eyes; however, the consensual response is blocked by pretreatment with guanethidine.

EXPERIMENT 2

The AUCs for both the normal and affected eyes of the four patients with Horner's syndrome on each of their three visits are shown on Table 2. The AUCs for both eyes on the saline study day were subtracted from those on the timolol study days to exclude the effects of diurnal variation.

When timolol was administered to the normal eyes a fall in IOP resulted, with AUCs ranging from 16·2 to 28·3 mmHg.min. in the treated eyes. A variable response was seen in the consensual, Horner's affected eyes with AUCs ranging from −4·5 to 12·9 mmHg.min. In only one subject was a convincing consensual ophthalmotonic reaction seen.

When timolol was administered to the affected eyes a fall in IOP occurred in that eye in only three of the four subjects. In two of these three a consensual ophthalmotonic reaction was seen in the fellow, normal eye.

Discussion

The results from experiment 1 show that, in a group of six ocular hypertensive subjects who display a significant consensual ophthalmotonic reaction to uniocular timolol administration, pretreatment of the consensual eye with guanethidine blocks the response. This result agrees with that found by Akagi *et al.*[3] In their experiments on animals, blockade of the cervical sympathetic on the side of the untreated eye inhibited the COR produced by an increase in IOP in the fellow eye. Their conclusion that the COR might be mediated by a nervous reflex with the efferent limb provided by the sympathetic nervous system is further supported by the findings of experiment 2, where, following timolol application to the normal eye, three out of the four Horner's syndrome patients showed a minimal COR in the sympathetically denervated eye. None of the present series of experiments support the findings of Perkins,[2] who in a small number of animals noted that sympathectomy on the contralateral side *facilitated* the COR.

Table 2 *Area under curve and integrated drug effect in mmHg.min after timolol and saline treatments to affected and normal eyes in patients with Horner's syndrome*

	Visit 1		*Visit 2*		*Visit 3*	
Eye	*Affected*	*Normal*	*Affected*	*Normal*	*Affected*	*Normal*
Treatment	*Timolol*	*Saline*	*Saline*	*Timolol*	*Saline*	*Saline*
AUC						
Subject 1	17 0	10·0	16 8	18·5	3·8	2·3
Subject 2	15·9	−8·2	5·1	10·0	1·4	−8 5
Subject 3	6·9	−12 0	10 1	31 8	8·1	7 1
Subject 4	25 7	11 4	−5 9	30 6	−1 4	2·3

	Visit 1 minus visit 3		*Visit 2 minus visit 3*	
Eye	*Affected*	*Normal*	*Affected*	*Normal*
Integrated drug effect				
Subject 1	13·2	7 7	12·9	16·2
Subject 2	14 5	0 3	3·7	18·5
Subject 3	−1·1	−19·1	2 1	24 7
Subject 4	27·1	9 2	−4 5	28 3

The Horner's syndrome patients also showed a poor COR in the normal eyes after timolol administration to the affected eyes. This could either be explained by postulating involvement of the sympathetic nervous system in the afferent as well as the efferent limb of the reflex, or it may be due to the reduced direct response to timolol seen in these eyes as compared with the normal eyes—a smaller direct response providing less stimulus for the consensual reaction. It is of interest to note that, in contrast to the present findings, Wentworth and Brubaker[4] found in their study of aqueous humour dynamics in patients with third neurone Horner's syndrome, that the direct response to timolol was the same for both normal and affected eyes.

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Retinal circulation during a spontaneous rise of intraocular pressure

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SUMMARY The retinal haemodynamic changes occurring in an eye with a spontaneous elevation of intraocular pressure were investigated by bidirectional laser Doppler velocimetry and monochromatic fundus photography. At an intraocular pressure of 47 mmHg the blood velocity and volumetric blood flow rate were significantly smaller and arterial blood velocity pulsatility was significantly greater than normal. The corresponding 88% reduction in perfusion pressure was accompanied by a 67% reduction in total retinal blood flow, indicating that autoregulation is not efficient at this level of intraocular pressure. An Octopus visual field examination obtained immediately following blood flow measurements suggested that the central retina can preserve a fairly good function under a total retinal blood flow rate of about one-third of the normal value.

The effect of an increased intraocular pressure (IOP) on retinal blood flow has been studied previously.[1-10] While some investigators have shown that retinal blood flow is maintained by autoregulation over a wide range of elevated IOPs,[2,3,10] others have found that blood flow is decreased at IOPs above 27–30 mmHg.[4-9]

In contrast to previous animal and human studies in which IOP has been artificially raised for short periods of time by cannulation of the anterior chamber or by application of a suction cup, this report describes retinal blood flow measurements obtained in an eye with a spontaneous and more prolonged elevation of IOP. These measurements were obtained by a combination of bidirectional laser Doppler velocimetry (BLDV) and monochromatic fundus photography.

Materials and methods

CASE REPORT

The patient studied was a healthy 25-year-old white male with nothing relevant in his medical or family history except for the occurrence of glaucoma in a paternal grandfather. The patient received routine ophthalmological care from age 6 to 20, and the results of his examinations were always within normal limits. The IOP recorded in his late teens was 20 mmHg in both eyes.

The patient's first significant visual complaints occurred at age 25. On repeated occasions following vigorous games of basketball he noted a fuzziness in his temporal field of vision in both eyes An ophthalmic examination revealed a visual acuity of 6/5 in both eyes and IOPs of 23 mmHg in the right eye and 26 mmHg in the left eye (Goldmann applanation tonometry). On slit-lamp examination marked iris transillumination was observed in both eyes. A faint Krukenberg spindle was noted in the left eye None was noted in the right eye. Gonioscopy showed very wide open angles, with minimal pigmentation in the right eye and heavy pigmentation in the left eye. Ophthalmoscopy revealed a cup to disc ratio of 0·4 in the right eye and 0·3 in the left eye. An octopus visual field (program 32) was within normal limits.

The patient was re-examined immediately after a vigorously played game of basketball. Ten minutes after the conclusion of the basketball game the IOP was 21 mmHg in the right eye and 29 mmHg in the left eye. No cells were noted in the anterior chamber of the right eye. Pigmented cells (+2 to +3) were noted in the left eye. Forty minutes after the conclusion of the basketball game the IOP was 28 mmHg and 34 mmHg. In the interval between these two intraocular pressure measurements the patient consumed approximately one quart (1·1 l) of water. At 120

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minutes after the basketball game the pressure was 20 mmHg and 47 mmHg. At this pressure central retinal artery pulsations were noted in the left eye, and the patient described a greying vision in the left temporal periphery.

After an explanation of the procedures, informed consent was obtained and retinal blood flow measurements by BLDV and monochromatic fundus photography were performed. Immediately after these measurements an Octopus visual field test (program 32) of the left eye was done. This test showed a mild depression of the superior periphery, with a mean sensitivity of 26·2 (SD 4) DB, a mean defect of 2·85 (SD 2·8) DB, and no localised visual field defect. The IOP measured in the left eye at the end of the visual field test was 50 mmHg. The brachial artery blood pressure was 125/75 mmHg. The IOP was returned to normal with acetazolamide 250 mg and timolol 0·5%.

Treatment was instituted consisting of one drop of pilocarpine 0·5% in each eye instilled one hour before playing basketball. On this therapeutic regimen the patient has experienced no further episodes of blurred peripheral vision. Examination after a game of basketball, with the use of pilocarpine, revealed no increase in intraocular pressure.

Retinal blood flow measurements were repeated three months later. At this time the visual acuity was 6/5 and the IOP was 19 mmHg in both eyes. No medication had been taken in the month preceding this visit.

METHODS

After pupillary dilatation with tropicamide 1% and neosynephrine hydrochloride 10%, a Polaroid colour fundus photograph of each disc was taken. BLDV measurements of the maximum or centreline velocity of red blood cells (V_{max}) were obtained from major retinal vessels in both eyes, as previously described.[11,12] For later reference the exact location of the measurement sites was marked on a Polaroid photograph.

V_{max} was determined according to the relation $V_{max}=K\Delta f$, where K is a constant related to the scattering geometry and the wavelength of the laser light, and $\Delta f=f_{1max}-f_{2max}$.[11,12] The cutoff frequencies of the Doppler shift power spectra recorded simultaneously in two different directions of the scattered light are f_{1max} and f_{2max}. In veins 10 pairs of power spectra were used to calculate an average Δf from which W_{max} was obtained.[11] Each of these spectra was recorded for 150 ms at random phases of the heart cycle and during different heart cycles. In arteries the pulsatility of V_{max} was defined as.

$$V_{max,syst}/V_{max,diast}=f_{1max,syst}/f_{1max,diast},$$

and was calculated for each artery by averaging the ratio $f_{1max,syst}/f_{1max,diast}$ obtained from an average of seven different cardiac cycles. $f_{1max,syst}$ and $f_{1max,diast}$ are the f_{1max} recorded during systole and diastole, respectively. Since the alignment of the fundus camera does not change during a heart cycle, Doppler power spectra recorded in only one direction of the scattered light are sufficient for the calculation of pulsatility.

To determine the change in red blood cell velocity during the heart cycle, the spectrum analyser was activated for 0·05 s at various phases of the cardiac cycle by means of an electronic gating module fed by the signal from a finger plethysmograph.

The cutoff frequencies of the Doppler shift power spectra were determined by visual inspection by an examiner who was masked with regard to the clinical condition of the subject studied and to the actual IOP at which the determinations had been made Following BLDV measurements, fundus photographs were taken in monochromatic light at 570 nm with a Zeiss fundus camera and Kodak Plus X panchromatic film.

The diameter (D) of veins and arteries at the site of the BLDV recordings was measured from projected photographic negatives with a calliper. Determinations of D were obtained from an average of the diameters measured from three photographs.

Owing to technical problems with the camera we obtained monochromatic photographs of only the upper hemisphere of the left eye on the visit at which the IOP was raised. Comparison of the diameters of five major vessels (three veins and two arteries) of the superior hemisphere between the two measurement sessions showed an average difference of only 0·16% (percentage changes of the diameter of the veins were +1·5%, −2·6%, and −0·5%, and in the arteries were +1·8% and −1·0%). Therefore, in the calculation of blood flows for the vessels of the lower hemisphere in which D could not be measured, we used the values of D determined from photographs obtained at normal IOP.

The retinal volumetric blood flow rate, Q was calculated from the relation·

$$Q=V_{mean}\cdot\frac{\pi D^2}{4}$$

where V_{mean} represents the mean velocity of whole blood. We have assumed that $V_{mean}=C\cdot V_{max}$, with C being a constant which is the same for all vessels measured. In this study we adopted a value of C=1/1·6, based on the work of Damon and Duling.[13] The exact value of C was not so important, since we were mainly interested in the changes in blood flow during elevated IOP.

IOP was determined by Goldmann applanation tonometry after the instillation of two drops of proparacaine HCl 0·5%. The brachial artery blood pressure was measured by sphygmomanometry.

The ophthalmic artery blood pressure was measured using compression ophthalmodynamometry. The IOP obtained during the application of a dynamometer force equivalent to the diastolic and systolic ophthalmic artery blood pressures was determined by applanation tonometry and recorded as $OABP_d$ and $OABP_s$. The mean ophthalmic artery blood pressure ($OAPB_m$) was calculated according to the formula $OABP_m = OABP_d + 1/3\ (OABP_s - OABP_d)$. Perfusion pressure (PP) was calculated as the $OABP_m - IOP$.

$OABP_m$ was measured only during the session in which resting IOP was normal. We have assumed in our calculations that $OABP_m$ was not different during the other measurement session from the fact that the mean brachial blood pressure did not change between the two occasions.

Results

Determinations of retinal vessel diameter, red blood cell velocity (V_{max}) and volumetric blood flow rate obtained at normal IOP (19 mmHg) and elevated IOP (47 mmHg) in the left eye are shown in Table 1. The exact locations of the measurements are depicted in figs 1A, B.

At elevated IOP, the venous volumetric blood flow rate and venous V_{max} were significantly decreased (Table 1). The total venous volumetric blood flow calculated by summing the flows in the individual major veins decreased by 67% from 31·0 (SD 5·0) µl/min to 10·1 (SD 2·3) µl/min.

In the right eye the sum of the venous volumetric flow rates measured in the three major retinal veins at normal pressure was 25·6 (SD 4·9) µl/min. As can be seen in Fig. 1, measurements of volumetric flow rate in the lower nasal vein were not performed. In this vessel a flow of 7 µl/min was estimated from the relationship between diameter and flow in normal eyes (Riva *et al.*[11] Fig. 4). From the measurements of the three major veins mentioned above and the estimation of flow in the lower nasal vein, we calculated a total venous volumetric blood flow rate of 32·6 µl/min.

At increased IOP, the velocity pulsatility measured from the lower temporal artery (10·2 (SD 2·6)) was significantly larger than normal (3·08 (SD 0·4)) Student's *t* test, $p<0·001$.

In the two arteries measured in the right eye at normal IOP (Fig. 1), vessel diameter (146 (SD 4) µm and 145 (SD 3) µm, respectively), and pulsatility (2·94 (SD 0·29) and 2·92 (SD 0·33)) were within the range of those measured in the left eye under similar conditions.

Table 1 *Retinal blood flow measurements in the left eye at normal and elevated intraocular pressure (IOP)*

	Measurements at normal IOP ±SD	*Measurements at elevated IOP ±SD*	*Percentage change*
IOP (mmHg)	19	47	+147
BABP (mmHg)	124/76	120/78	—
OABP (mmHg)	66/44	—	—
PP_m (mmHg)	32	4	−88
Vein 1			
Diameter (µm)	169±4	(169)*	—
V_{max} (cm/s)	1·41±0·36	0·38±0·1	−73†
Q (µl/min)	11·9±3·1	3·2±0·8‡	−73
Vein 2			
Diameter (µm)	170±3	161±4	−5
V_{max} (cm/s)	0·94±0·31	0·37±0·26	−61†
Q (µl/min)	8·0±2·6	2·8±1·9	−65
Vein 3			
Diameter (µm)	132±1	129±3	−2
V_{max} (cm/s)	1·47±0·56	0·49±0·12	−67†
Q (µl/min)	7·5±2·9	2·4±0·7	−68
Vein 4			
Diameter (µm)	109±3	(109)*	—
V_{max} (cm/s)	1·02±0·23	0·49±0·15	−52†
Q (µl/min)	3·6±0·8	1·7±0·5‡	−53
Total venous Q	31·0±5·0	10·1±2·3	−67

*These values could not be measured (see 'Methods'), and therefore, we used the results obtained during normal IOP †Significant change by non-paired Student's *t* test, $p<0·001$ ‡This value was calculated from the venous diameter measured at normal IOP

BABP indicates brachial artery blood pressure, systolic/diastolic; OABP, ophthalmic artery blood pressure, systolic/diastolic, PP_m, mean perfusion pressure, V_{max}, centreline (maximum) velocity of red blood cells, Q, volumetric blood flow rate

The changes in the red blood cell velocity during the heart cycle under normal and elevated IOP are shown in Figs, 2A, B. At high IOP the diastolic V_{max} is close to zero, and the systolic peak is considerably narrower than that present at normal IOP. Ophthalmic artery diastolic and systolic blood pressures measured during the session in which IOP was normal were 44 mmHg and 66 mmHg, respectively.

Discussion

Our results show that an 88% decrease in perfusion pressure (IOP=47 mmHg) induces a reduction in total volumetric blood flow rate of about 67%. Thus the retinal vasculature behaves almost like a passive system. Under such an acute decrease in perfusion pressure a normal retina would show a reduction in blood flow of only approximately 40%[9] due to autoregulation – that is, the tendency of the retinal circulation to maintain a nearly constant blood flow in spite of changes in perfusion pressure. This suggests that under a more prolonged increase in

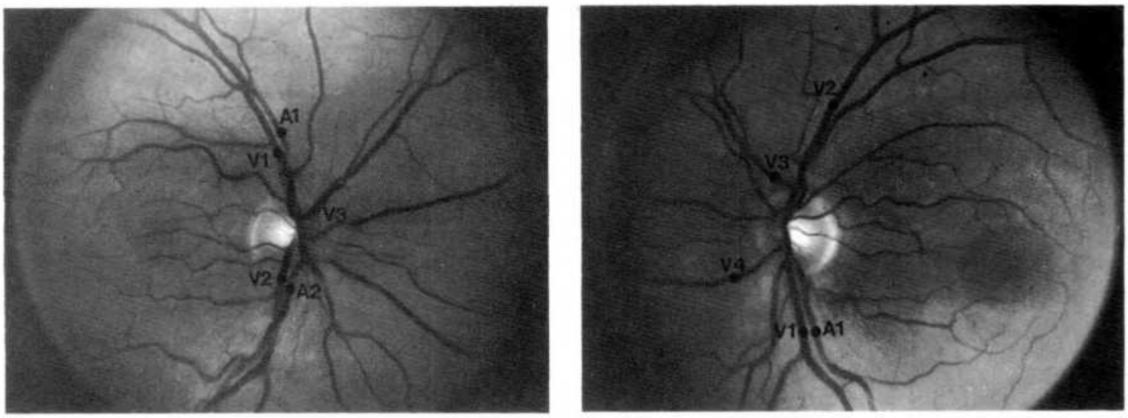
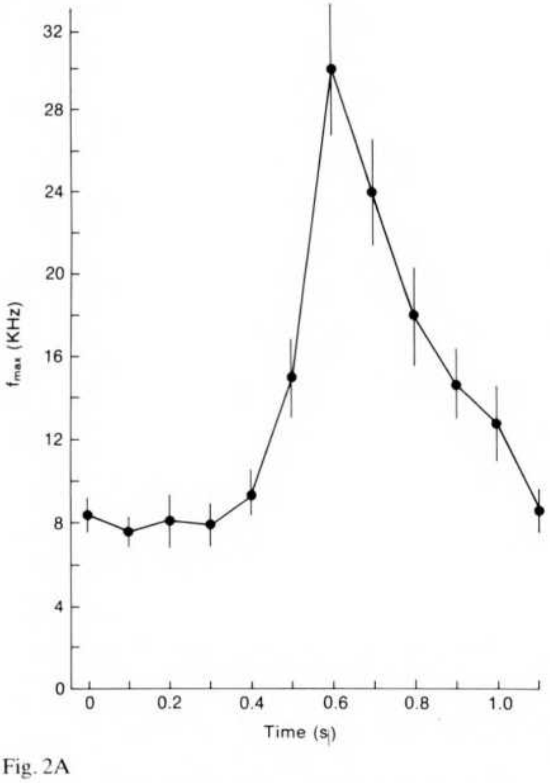


Fig. 1A

Fig. 1B

Fig. 1 *Monochromatic fundus photographs of the right eye* (A) *and the left eye* (B) *obtained at normal intraocular pressure. Dots indicate measurement sites or veins* (V) *and arteries* (A).



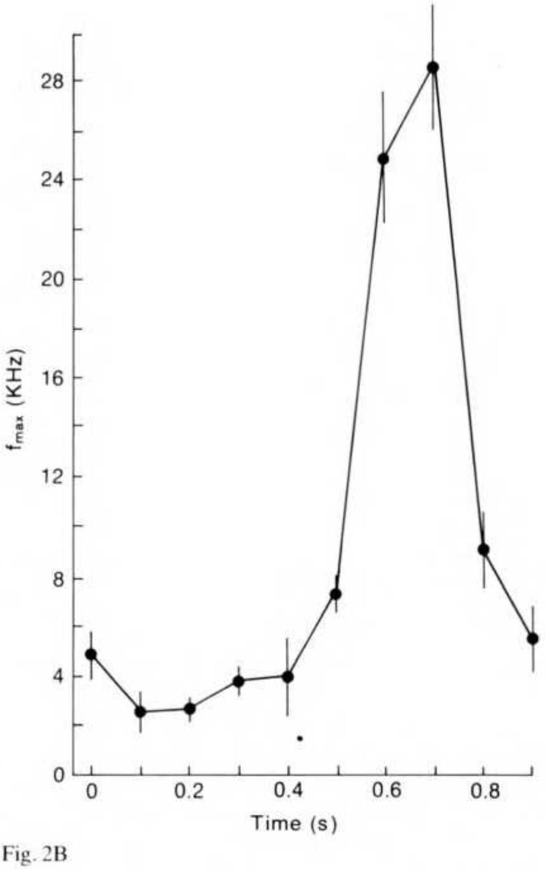


Fig. 2A

Fig. 2B

Fig. 2 *Variations of* $f_{max} \propto V_{max}$ *during the cardiac cycle at* $IOP = 19\ mmHg$ (A), *and at* $IOP = 47\ mmHg$ (B). f_{max} *is the cutoff frequency of the Doppler shift power spectrum recorded in one of the two scattering directions obtained during bidirectional laser Doppler velocimetry. Error bars represent ±1 SD based on six measurements.*

IOP the autoregulatory response may become less efficient.

As can be seen in Table 1, during elevated IOP the percentage changes in V_{max} and volumetric blood flow rate were smaller in vein 4 (inferior nasal) than in the other veins. The differences between the individual veins, however, were not statistically significant, and therefore we cannot conclude that the regulation may be more efficient in one area of the retina than in another.

The results of the present study are in accordance with previous reports in which the acute effect of a large increase in IOP was studied in the human[6-9] and animal[1,3,5,10] retina. The total retinal venous volumetric blood flow measured at normal IOP in the left eye (30·8 μl/min) is similar to that determined in the right eye (32·6 μl/min), and both are very close to the values reported previously in normal human retina.[11]

Our measurements also show that under elevated IOP there is an increase in arterial velocity pulsatility. Arterial velocity pulsatility, calculated as the ratio $V_{max,\, syst}/V_{max,\, diast}$, increases when the IOP is raised to a level close to the ophthalmic artery diastolic pressure, because V_{max} approaches zero during diastole. This effect can be seen in Fig. 2, which shows that at an IOP of 47 mmHg blood velocity is minimal during most of the heart cycle. Only during systole is there an increase in blood velocity for a relatively short period of time.

The case reported here has offered us a unique opportunity of investigating the retinal haemodynamic changes that occur in a human eye with spontaneously elevated IOP. In contrast to previous reports in which the IOP has been artificially elevated either by cannulation of the anterior chamber or by application of a suction cup, in the present study no manipulation of the eye was performed. In addition, the IOP in the present case remained elevated for two to three hours, allowing us to investigate the effect of a more prolonged increase in pressure than that achieved in most of the previous investigations.

It is interesting to note that, in spite of the marked reduction in retinal volumetric blood flow rate, visual field examination by Octopus perimetry revealed only a mild sensitivity depression within the central 30° field, which could be due in part to the bleaching of visual pigments produced by the illumination of the BLDV instrument. This suggests that, although the retina has a high metabolic rate and a large oxygen extraction from blood, the central retina is still capable of preserving a fairly good visual field function as measured by Octopus despite a marked decrease in total retinal blood flow. The obscuration of the temporal field reported by the patient, on the other hand, shows that the peripheral visual function is not normal at this reduced rate of total retinal blood flow.

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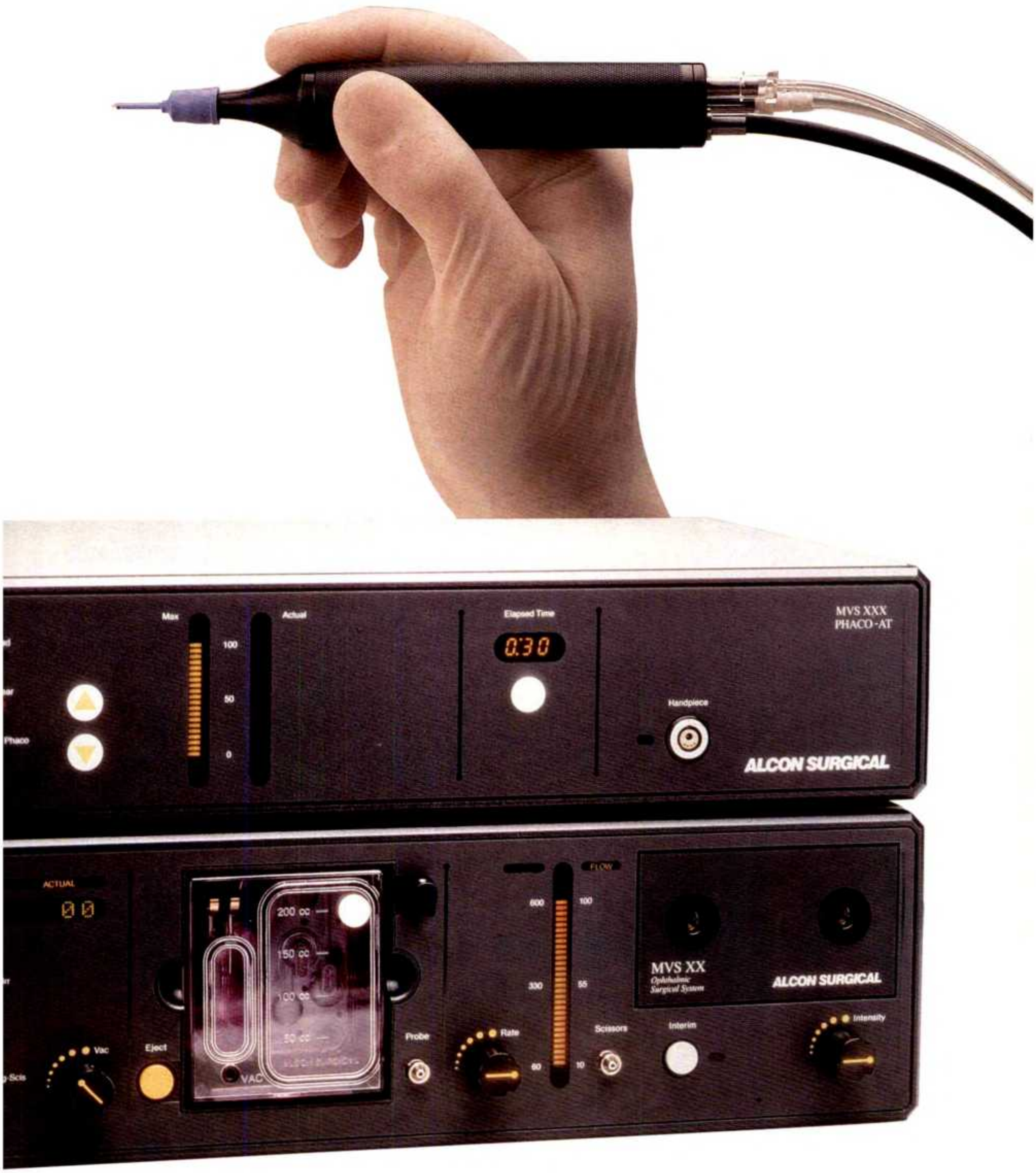

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Stereoscopic evoked responses to crossed and uncrossed disparity accompanying simulated refractive error

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SUMMARY Evoked potentials were recorded to the occurrence of a disparate stimulus in dynamic random dot stereograms. Seven adult males, all of whom had vision which was normal or corrected to normal, participated in the experiment. Subjects viewed 100 ms duration stimuli which embodied 30 arc min of either crossed or uncrossed disparity under four conditions of spherical overcorrection: −0·25, +1·0, +2·0, +3·0 dioptres. The first condition, essentially normal refraction, yielded reliable behavioural reports of the stimulus and clear evoked potentials to both crossed and uncrossed disparity. With increasing overcorrection the behavioural reports became less reliable, and the evoked potentials were degraded for both conditions of disparity. The responses to the crossed disparity condition, however, showed significantly less degradation in both behavioural and electrophysiological measures. The implications of this finding may be that there are separate cortical subsystems for the processing of crossed and uncrossed disparity and that the former is more robust under non-ideal viewing conditions.

The human visual system processes the differences between the images formed on the spatially separated right and left retinae and uses the differences in forming a single, fused, three-dimensional image. These differences can be considered in angular terms. As a first approximation light rays travel straight from an object of interest through the nodal points of the eyes to the retinae, as illustrated in Fig. 1. Let the angle between the fixation rays be called angle F and between the rays emanating from the object of interest be angles X_1, X_2, etc. If angle X_1 is equal to angle F, then the object lies on the horopter, that is, it lies in the fixation plane. The angle X_1 is greater than angle F, and the image of the object is said to produce a crossed disparity, because rays carried through to the horopter from the right eye pass the fixation point to the left and vice versa. The angle X_2 is less than angle F, producing an uncrossed disparity.

Microelectrode studies have shown that in monkeys there are separate groups of cortical neurones dedicated to the processing of crossed and uncrossed disparity.[1 2] It is likely that such neuronal groups also exist in man. These groups are a part of a human stereoscopic visual system which serves at least two functions: (1) it allows the observer to judge precisely the position of objects, relative to some fixation point, within the visual field; (2) it aids the observer in the estimation of direction and velocity of objects which are moving within the visual field. On an intuitive level it would seem more important for an observer to judge correctly the position and speed of an object which is approaching than of one which is moving away. It is suggested, therefore, that the ability to process changes in disparity, in cases where the change is in the crossed disparity direction, will be found superior to the uncrossed disparity counterparts. It is further suggested that crossed disparity processing will be found more robust under non-ideal viewing conditions, such as may arise in the presence of a significant refractive error. The first hypothesis received strong support from a behavioural study[3] in which measures of minimum presentation times for the detection of disparate stimuli showed significant crossed/uncrossed disparity differences. The hypothesis also received support from an electrophysiological study in which responses to crossed and uncrossed disparities were recorded in the upper,

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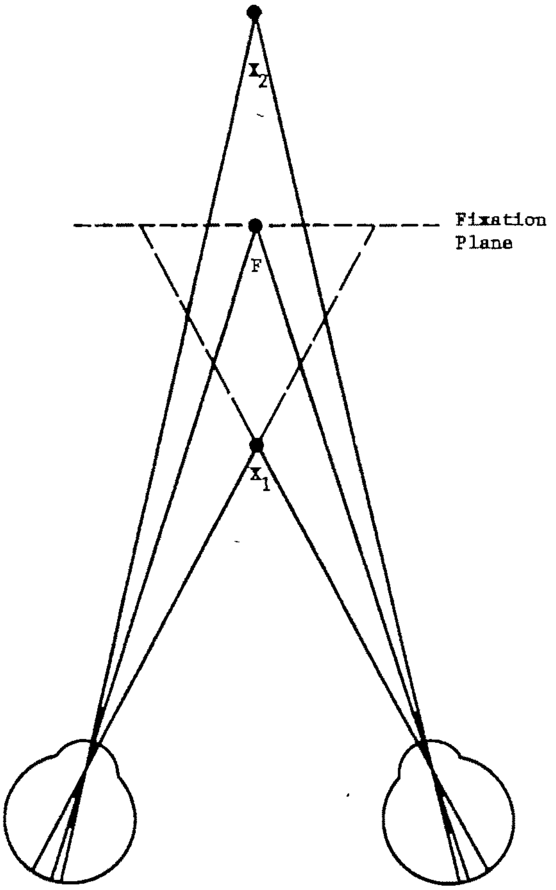

Fig. 1 *Illustration of crossed and uncrossed disparity. The difference (F-X_1) represents a crossed disparity, while (F-X_2) represents an uncrossed disparity.*

centre, and lower visual fields.[4] The aim of this paper is to test the second hypothesis by investigating the electrophysiological responses to the introduction of crossed and uncrossed disparity under conditions of simulated refractive error.

Material and methods

Visual stimuli comprised dynamic random dot stereograms. These were presented in a point-to-point display mode on separate (left and right) Tektronix 602 display units (P31 phosphor). The display units were supported vertically on trolleys which were attached to the moving arms of a Clement Clarke synoptophore.[5] The images of the display units were reflected into the eyepieces via front-surfaced, half-silvered mirrors. Fixation points, subtending 0·14° and illuminated by red LEDs, were positioned centrally at the fixation distance behind the mirrors.

The random dot display, generated by a computer controlled, hardwired unit,[4] comprised a 256×256 pixel square matrix subtending 10·7° on the side. The disparate stimulus, when present, was located centrally. It was a square, subtending 3° on the side and with a disparity of 30 arc min. By interchanging the left and right displays a crossed or uncrossed stimulus could be created. It should be noted that, unlike real space tests, there were no optical differences between the two disparity conditions. Dot presentation rate was 100 000 point pairs per second.

Subjects. Seven male subjects, ages 32·6 (SD 7·3) years, all right handed and with normal or corrected to normal visual acuity, volunteered to participate in the experiment.

Electrophysiological responses were recorded from four scalp sites: 02,01,T6,T5 (International 10-20 System) and referenced to Fz10, a midline site 10 cm posterior to the nasion. Eye movements were monitored from a single channel by means of electrodes placed diagonally across the eyes. Chlorided silver electrodes were used (Burden type), and scalp impedances were kept at 3 kOhms (±10%) throughout the experiment.

Data were recorded at a rate of one five-channel sample every four milliseconds for a one second epoch. Low-pass filters were set at 30 Hz (3 dB down) and high-pass at 0·5 Hz.

The Experiment. Subjects were screened for visual acuity with a Snellen chart. They then underwent a series of static stereopsis tests involving the Randot (Stereo Optical Co.), Neill Stereo Wedge (Clement Clarke), and synoptophore numbered shapes (Clement Clarke, slides D21,22) tests. In order to facilitate correct fusion, visual alignment was checked on the synoptophore with Mayou No. 2 simultaneous perception slides. All subjects were within normal limits on every test.

Subjects were seated in a comfortable viewing position in a light-attenuated room. The synoptophore eyepieces were initially arranged with a −0·25 dioptre allowance for instrument accommodation. The instrument therefore had an optical viewing distance of 4 m. The subject viewed 32 presentations each of the crossed and uncrossed disparity conditions, along with four other 32-trial conditions reported elsewhere.[4] Separate averaged evoked potentials were recorded for each of these conditions. The eyepiece lenses were then replaced with pairs of lenses which were either +1·0, +2·0, or +3·0 sphere dioptres over-power. Four sets of the 32-trial averages were then recorded for each of the central crossed and uncrossed stimuli, the order being randomised. This group of trials was repeated twice more with different pairs of eyepiece lenses each time. The order of selection of lenses was randomised across subjects. Finally, the −0·25 dioptre lenses were replaced and three more sets of the averages recorded, along with 12 other conditions.[4] Thus four sets of 32-trial averages were recorded for all conditions. The stimulus onset, comprising the abrupt introduction of disparity, occurred 100 ms into the recording epoch, and the duration of the disparity was 100 ms.

A PDP 12 computer controlled the experiment, recorded and stored electrophysiological responses, and was responsible for the performance of off-line data processing.

Data analyses. For each subject and each condition the four sets of 32-trial averages were combined into 128-trial superaverages. These were then normalised across the 100 ms prestimulus interval. The mean amplitudes were then calculated across a 100 ms window commencing 200 ms post stimulus. The mean amplitudes were then entered into a 4 (dioptre)×2 (crossed/uncrossed)×4 (site) analysis of variance (ANOVA). In order to test the relationship between amplitude of response and degree of refractive defocusing, an amplitude versus dioptre linear regression was performed on each subject's data and the slope estimates of the regression lines were submitted to a 2 (crossed/uncrossed)×4 (site) ANOVA.

Results

BEHAVIOURAL

All subjects were able to identify the onset and orientation of the crossed stimulus for all refraction conditions, though they reported some difficulty in the +3·0 dioptre condition. All subjects, furthermore, correctly reported seeing the uncrossed stimulus in the −0·25 dioptre condition, and six correctly described the +1·0 dioptre condition. Only two subjects, however, could reliably identify the presence of the uncrossed stimulus in the +2·0 dioptre condition, and no subject reported seeing this stimulus in the +3·0 dioptre condition.

ELECTROPHYSIOLOGICAL

The superaveraged evoked responses for each of the conditions are included in Fig. 2 (sites 02, 01 only). Two trends are evident from the diagram and are confirmed by ANOVA. The responses to both crossed and uncrossed stimuli became smaller as the degree of simulated refractive error increased, the main effect for dioptre being significant (F (3,18)= 9·93, $p<0·0004$). The responses to the uncrossed stimulus, furthermore, were smaller overall than those to the crossed stimulus (respective mean amplitudes −1·3 and −2·0 microvolts), the main effect for

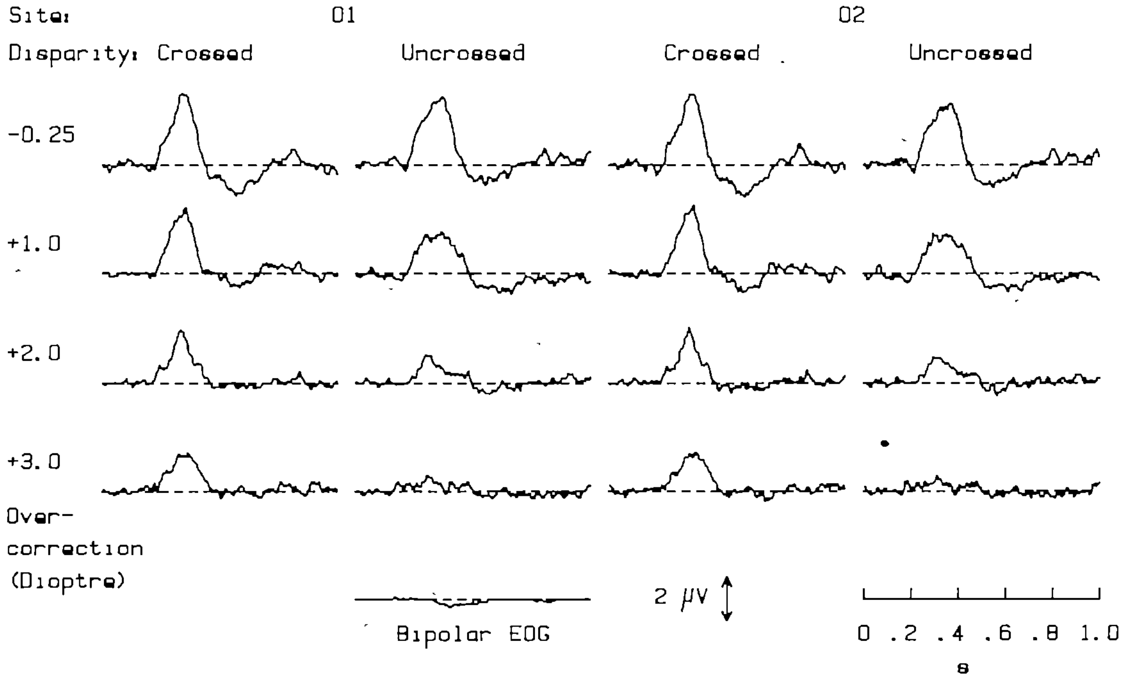

Fig. 2 *Superaveraged evoked responses (sites 01 and 02, Negative up) to the crossed and uncrossed disparity across all refraction conditions.*

crossed/uncrossed also being significant (F (1,6)= 26·07, p<0·003). The remaining main effect, site, was not significant.

Another trend evident in Fig. 2 is that the responses to the uncrossed stimulus were more heavily attenuated by the over-refraction than those to the crossed stimulus. In the normal viewing condition (−0·25 dioptre), the responses were of similar size (crossed=−2·6, uncrossed=−2·4 microvolt). For the +3·0 dioptre condition, however, the responses were quite different in size (crossed= −1·5, uncrossed=−0·3 microvolt). Indeed the uncrossed condition evoked almost no response at all. This trend is illustrated well in Fig. 3, which shows the relationship between amplitude and simulated refractive error. The regression line for the crossed condition has a slope of −0·37 microvolts/dioptre, whereas that for the uncrossed condition is −0·65 microvolt/dioptre. The linearity of both regression lines, which comprise the data for the four channels combined, is significant (BMDP program P1R[7]: crossed: F (1,110)=12·64, p<0·0006; uncrossed: F (1,110)=55·36, p<0·0001). The main effect for crossed/uncrossed was significant in the ANOVA of the slopes (F (1,18)=6·59, p<0·05).

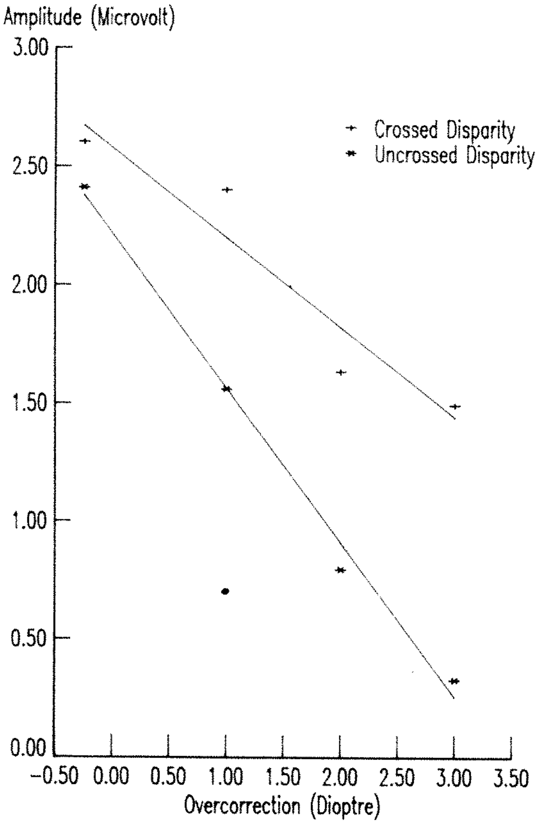

Fig. 3 *Amplitude of response is plotted against refractive overcorrection, along with the associated lines of best fit.*

Discussion

The results of this experiment, both behavioural and electrophysiological, provide strong support for the hypothesis under test. The introduction of a simulated refractive error effectively diminishes the observer's ability to discriminate high-frequency textual detail, which in turn affects stereoscopic resolution. The effect on the ability to resolve changes in uncrossed disparity is significantly greater than the crossed disparity counterpart. The visual system therefore appears to be especially sensitive in the processing of crossed disparity. The result must be qualified by the following comments. Firstly, the experiment was based on the artificial simulation of a myopic type of refractive error in subjects with essentially normal vision. It will be interesting to repeat the experiment with real myopes to see if progressive refractive correction differentially *improves* the stereoscopic resolution. Secondly, within the confines of the experimental run it was impracticable to use accommodation blocking drugs. The subjects therefore responded to under-power eyepiece lenses by simply accommodating. Hence, while it would certainly have been desirable to do so, it was not possible to test responses to simulated hypermetropia.

In this experiment the dynamic random dot stimulus comprised a change from zero disparity to disparity and back to zero disparity. At onset this change in disparity was interpreted as a movement towards the viewer in the crossed condition and away in the uncrossed condition. A previous study by one of the authors[8] has shown that the onset of disparity is responsible for the bulk of the recorded response.

Despite the fact that no subject could perceive the stimulus in the +3·0 dioptre, uncrossed disparity condition, a small but consistent evoked response was recorded, as can be seen in Fig. 2. A previous study has shown that this is very unlikely to be artefactual in origin.[9] The result is consistent with that of an earlier study[10] in which a group of non-perceiving subjects produced measurable stereoscopic evoked potentials. The normal response appears to reflect an overlay of processes such as those related to form detection[10] and to the processing of edge details,[9] along with more fundamental stereoscopic functions. The conditions imposed on the subjects by the combination of +3·0 dioptre refractive error and uncrossed disparity apparently rendered many, but not all, of these processes inoperative.

As an object approaches an observer, the accommodation/convergence reflex assists by keeping the object within the range of focused single vision. A quickly approaching object will generally lead the accommodation and convergence process. Hence the image of the object will be (*a*) somewhat blurred owing to the delay in the accommodation process, and (*b*) it will be associated with a crossed disparity due to the trailing convergence process. The findings of this experiment indicate that the visual system is particularly well adapted to cope with this situation.

The result may also have some implications in relation to the properties of vision in squint. A convergent squint results in the observer viewing the world through an inappropriate uncrossed disparity, while a divergent squint results in an inappropriate crossed disparity. The functional consequences of these differences are not clear. Further investigation is certainly warranted.

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Medulloepithelioma (diktyoma)

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SUMMARY Sixteen cases of medulloepithelioma are described. Clinical data and follow-up were available on 15. Four patients underwent iridocyclectomy initially; all later needed enucleation and one had an orbital recurrence. The remaining 12 patients underwent primary enucleation. All 15 patients with follow-up are alive with no evidence of tumour recurrence. It is suggested that enucleation be performed for all but the most localised tumour. Rubeosis was noted in 13 of the 16 eyes, and this may assist in making the diagnosis. The World Health Organisation histological classification of medulloepithelioma was applied, but some problems were encountered, particularly where the presence of heteroplastic brain tissue was used as a criterion for teratoid tumour and where rosettes were used as a criterion for malignancy.

Medulloepithelioma is an uncommon tumour which arises from undifferentiated non-pigmented ciliary epithelium and which usually presents in childhood. Very rarely it may arise in optic nerve or retina. The tumour is pleomorphic and diagnosis is often delayed.

The tumour usually grows slowly and may be locally malignant. Distant metastasis is uncommon and has been described only in cases where orbital spread has occurred. Broughton and Zimmerman[1] have contributed most to the current understanding of the clinical spectrum and histological classification of the disorder. They reviewed 56 cases derived from the records of the Armed Forces Institute of Pathology (AFIP). Clinical follow-up data were available on 33 of them. Andersen[2] reported a series of 23 cases, about half of which were on record at the AFIP. Reese[3] and Shields[4] have reviewed the subject. Most other publications on medulloepitheliomas comprise single case reports with or without a review of the literature.

This paper presents the histological features of 16 cases of the tumour on record at the Institute of Ophthalmology in London. Clinical data and follow-up information were available on 15 patients. Only two of these patients have previously been the subject of case reports.[5,6]

Patients and methods

Over 25 years there have been 16 cases of histologically confirmed medulloepithelioma in humans on file at the Institute of Ophthalmology for which complete biographical data are available. For the purposes of this study all tissue specimens were reviewed and fresh slides made as appropriate. Attending clinicians and pathologists were contacted for further details and current follow-up status. All but one case has been treated within the United Kingdom.

Pertinent biographical data are presented in Table 1. There were nine females and seven males. The ages at diagnosis ranged from 6 weeks to 48 years and the follow-up from three months to 25 years.

Results

CLINICAL FEATURES

The presenting symptoms are detailed in Table 2 and the pretreatment signs in Table 3. The surgical management and histological classification of the surgical specimens are recorded in Table 1. Twelve cases had primary enucleation and all were alive without clinical tumour recurrence. Three of these had extrascleral extension of the tumour, one of whom received adjuvant radiotherapy. These three patients have been followed for between 5 and 11 years.

Four patients initially had iridocyclectomies, either in order to make the diagnosis or in an attempt to excise the tumour. All four have since required enucleation — two for recurrent intraocular tumour, one for reduced vision and pain, and one for rubeotic glaucoma. One of these patients, with persistent intraocular tumour, had recurrent tumour in the

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Table 1 *Biographical data, management, and histological classification*

Number	*Age at diagnosis*	*Sex M/F*	*Follow-up duration*	*Management*	*Histology*
1	3 yr	M	25 yr	Enucleation	NT B
2	14 yr	F	18 yr	Enucleation	NT B
3	48 yr	M		Enucleation	T B
4	2 yr	M	13 yr	Enucleation	T B
5	11 mth	F	11 yr	Enucleation	NT B
6	8 mth	F	11 yr	Enucleation	NT M (invasive)
7	1 yr	M	13 yr	Iridocyclectomy Enucleation Exenteration+DXT	T M (neuroblastoma)
8	2 yr	F	13 yr	Iridocyclectomy Enucleation	NT M (invasive)
9	6 mth	F	11 yr	Iridocyclectomy Enucleation	NT M (astrocytoma)
10	13 yr	F	12 yr	Enculeation	NT B
11	6 wk	M	5 yr	Enucleation	T M (invasive)
12	14 yr	F	5 yr	Enucleation	NT B
13	10 yr	M	2 yr	Enucleation	T B
14	5 mth	M	5 yr	Enucleation DXT	T M (neuroblastoma, embryonal sarcoma)
15	2·5 yr	F	6 mth	Iridocyclectomy Enucleation	T B
16	4 yr	F	3 mth	Enucleation	T B

T=teratoid. NT=non-teratoid. B=benign M=malignant

orbit two years after enucleation. This was treated with exenteration and radiotherapy. The patient had no further clinical metastasis after 11 years. The other three all had tumour cells at the site of the previous surgical section when the whole eye was examined, but the patients have remained clinically free of tumour. Two have been followed up for 11 years and one for six months.

HISTOLOGICAL FEATURES

Sixteen cases were reviewed. Ten were benign, of which seven were non-teratoid. Of the six malignant cases two were aggressively invasive preoperatively. Both were non-teratoid. The teratoid elements found included cartilage in three, and brain (neurones and glia) in two. Some unusual, but not teratoid, elements were also found—angioma in one and ganglion cells in another. No rhabdomyoblasts were found in any of the 16 cases. Most tumours contained rosettes of various types. Cystic change with accumulation of mucopolysaccharide material was seen in three cases. Unequivocal cytologically malignant areas contained neuroblastoma-like tissue in two, embryonal sarcoma-like tumour in one, and astrocytoma in one Calcification was present in four cases.

Table 2 *Presenting symptoms*

Symptom	*No of patients*
Anterior chamber/iris mass	6
Reduced vision	4
Photophobia/epiphora	2
Leukocoria	1
Abnormal pupil	1
Enlarging globe/exophthalmos	2
Heterochromia	1
Squint	1

Table 3 *Pretreatment signs*

Sign	*No. of patients*
Cataract	8
Rubeosis	13
Glaucoma	8
Anterior chamber/iris mass	6
Retinal mass	2
Squint	1
Enlarged globe	1
Exophthalmos	1
Iritis	1
Retinal detachment	2
Incidental finding—traumatic ruptured globe	1

Discussion

Medulloepithelioma was first recognised and termed 'carcinome primitif' by Badel and Lagrange in 1892 [7] Verhoeff described another case in 1904.[8] He gave it the name 'teratoneuroma', although his case contained no teratoid elements. Fuchs reported an example in 1908[9] in which the predominant histological feature was a net-like pattern of poorly differentiated cell ribbons, and he used the term 'diktyoma' derived from the Greek root for 'net'. This name makes up in brevity what it lacks in its description of cytological or embryological features, and for years was the most popular term for this tumour. The term 'medulloepithelioma' was first applied in 1931 by Grinker.[10] The etymology of these various terms has been discussed elsewhere.[1]

PATHOLOGY

Quite recently the classification of tumours arising from the ciliary epithelium has been simplified, largely through the efforts of Zimmerman. His classification has been adopted by the World Health Organisation.[11] Tumours of the ciliary epithelium are divided into congenital (arising from undifferentiated epithelium and presenting commonly in childhood) and acquired (arising from differentiated epithelium and presenting commonly in adults). Undifferentiated cells do not normally persist in the ciliary epithelium into adulthood. All congenital ciliary epithelial tumours are medulloepitheliomas. The acquired group includes hyperplasias, adenomas, and adenocarcinomas.

The diagnosis of medulloepithelioma of the ciliary body is not usually difficult histologically, but classification into the simple and elegant categories of Broughton and Zimmerman[1] may prove harder. The classification splits the tumours into benign and malignant on the basis of cytological features and invasive, rather than metastatic, properties. The latter is not a contentious issue, since these tumours are often locally aggressive and may spread to involve the orbit as well as other intraocular structures. The former set of criteria, involving pleomorphism, mitotic rate, and degree of undifferentiation, are less easy to apply, since these tumours are by definition immature and may be growing quickly. Sheets of basophilic cells may resemble neuroblastoma or undifferentiated retinoblastoma in otherwise unremarkable tumours. Rosetting is not necessarily a helpful diagnostic feature, since 81% of cases in the present series had rosettes, some of the more primitive retinal anlage type, others more like Homer-Wright rosettes, and others with clearly delineated external limiting membranes around a central lumen, resembling Flexner-Wintersteiner rosettes. Occasionally the rosettes have turned 'inside-out', and both of the latter types of rosettes resembled those seen in dysplastic retinas, especially those associated with trisomy 13–15.

It is interesting that heteroplastic cartilage is also associated with this trisomy and with some microphthalmic eyes. This is the most easily recognised heteroplastic or teratoid element. In the present series only two tumours had mature cartilage. Recognition of genuinely teratoid elements can be difficult. In several of our cases areas which appeared to be 'brain' were in fact composed only of glial elements, many showing the well described spongioblastic change, while some appeared gemistocytic. Unequivocal neurone cell bodies were rare but were seen in two cases. We did not regard ganglion cells as being teratoid. Other glial concomitants such as Rosenthal fibres were seen, and one tumour contained frank astrocytomatous areas. Rhabdomyoblasts were seen in one specimen at the Institute of Ophthalmology from a patient on whom biographical data were not available, but not in any of the 16 documented cases reported here.

These tumours present a spectrum of malignancy. While most behave well, without overt aggressive invasion, the AFIP series included four deaths from tumour.

CLINICAL FEATURES

Rubeosis was a clinical or histological feature of 13 of the 16 cases in this study, as compared with only 11 of 56 cases in the AFIP series. It may be a useful confirmatory sign when making the diagnosis. We know of no work on angiogenic factors in these tumours.

The life expectancy of treated patients is very good. In the present series all 15 patients with follow-up are alive, with no evidence of residual tumour. All affected eyes had been removed, however. In the AFIP series the presence of orbital involvement was a major determinant of survival,[1] though the present series includes survivors even with extrascleral extension of tumours containing cytological evidence of malignancy.

The best treatment for these patients is uncertain. The tumour is too uncommon for any one centre to have acquired much experience in different therapeutic strategies. Broughton and Zimmerman suggest that local excision be attempted for small, well circumscribed tumours. They base this recommendation on two patients who had had excision iridocyclectomies with no apparent tumour recurrence after a follow-up of between 1 and 22 years. The age of the patients at treatment is not given, nor is their subsequent visual function or the presence of cataract, rubeosis, glaucoma, or squint. Given the usual onset of these tumours in early childhood, one might anticipate that such surgery would result in significant amblyopia. Furthermore, it is not clear whether complete excision of the tumours was achieved: the possibility of corneoscleral extension, which is one of the criteria of malignancy, may have been difficult to exclude.

In the same series, eight eyes which had undergone iridectomy or iridocyclectomy as an initial procedure required later enucleation, making the overall chance of retaining the eye after such surgery 20%. The tumour is typically friable and difficult to manipulate surgically. Although about one-half of the tumours contain melanin pigment microscopically,[1] they are often not clinically pigmented. This makes definition of the posterior extent of the tumour by transillumination more difficult. The attendant rubeosis increases the risk of peroperative intraocular haemorrhage.

Broughton and Zimmerman[1] remarked on the frequency with which highly malignant looking areas within the tumour appeared to be confined by benign tumour, and they considered that this might retard the clinical expression of malignancy. Surgical manipulation might adversely affect such a balance. The prognosis for tumours confined within the globe is uniformly excellent: no case of tumour death has been recorded without evidence of orbital involvement.

All these factors militate against attempting local excision of all but the most circumscribed tumours, given the limited chance of anatomical and functional success of the operation and the potential for promoting orbital recurrence.

We know of no data on the treatment of ocular medulloepithelioma by radiotherapy, though the central nervous system counterpart of the tumour is known to be radiosensitive. While it would be technically feasible to treat ocular medulloepithelioma by local radiotherapy employing a radioactive scleral plaque or a proton beam, the rarity of the tumour and the difficulty in establishing the diagnosis clinically would suggest that a pretreatment tissue diagnosis would be required for the proper assessment of the approach. The potential hazard of intraocular biopsy of a locally aggressive tumour and the difficulty of obtaining a tissue sample representative of the entire tumour would also hamper the investigation of this option.

We recommend that enucleation should be the primary treatment for most cases. Where a credible non-neoplastic differential diagnosis exists, incisional biopsy may be considered with a view to subsequent radiotherapy for localised tumours and enucleation for extensive tumours.

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Analysis of the factors involved in cosmetic failure following excision of the eye

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SUMMARY We graded the overall cosmetic outcome of 56 patients who required excision of the eye. Each patient was then subjected to a more detailed analysis of the specific abnormalities associated with excision of the eye in order to discover which are associated most consistently with a poor cosmetic result. The only factor showing a statistically significant variation with the overall cosmetic outcome was the degree of upper lid sulcus. Taken individually the other features showed no statistically significant correlation. When each finding was scored, the averaged sum of the scores was related to cosmetic outcome with statistical significance. A method of quantifying orbital volume loss is described.

Excision of the eye is indicated for inoperable intraocular malignancy, when there is a substantial risk of sympathetic ophthalmitis, endophthalmitis with failed treatment, and for a blind, painful eye.[1] As there is such a wide variation in cosmetic outcome, it would be an advantage to know the features associated with cosmetic failure. It might then be possible to alter methods of excision in order to reduce their incidence. This would in turn reduce the need for subsequent corrective procedures.

Some features associated with excision of the eye are well known. Enucleation in childhood results in a reduced orbital volume.[2-4] In adults there is a reduction in orbital volume which is either immediate or may be delayed.[2-4] Excision of the eye is said to be associated with the development of an upper lid sulcus, and this has stimulated the introduction of many varied surgical corrective techniques.[5-8] Movement of the artificial eye, even with the better magnetic implants, is relatively poor. Cosmetic result and movement are said to be better when an orbital implant is used after enucleation[5,9,10] or after evisceration.

To discover more about the factors associated with poor cosmetic outcome we examined a group of patients who had undergone excision of the eye. Our aims were as follows: (1) to determine whether the apparent orbital volume loss which exists after excision of the eye could be measured clinically; (2) to assess the contribution of any other detectable anatomical or functional abnormalities to overall cosmetic result; (3) to determine whether the presence of an orbital implant was associated with a better overall cosmetic result; (4) to determine whether cosmetic outcome was influenced by the choice of excision procedure (evisceration rather than enucleation); (5) to see if age, sex, and aetiology were related to cosmetic outcome.

Materials and methods

From the Birmingham and Midland Eye Hospital operating theatre register we obtained the details of each patient who had undergone excision of the eye

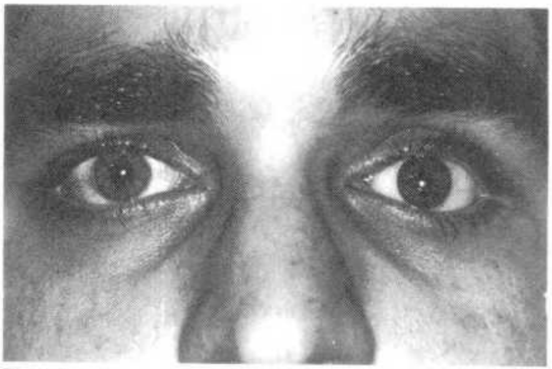

Fig. 1A

Fig. 1 *Photographs taken in primary position* (A), *looking right* (B), *and looking left* (C).

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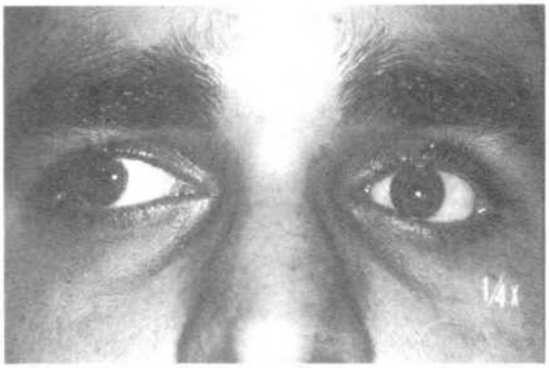

Fig. 1B

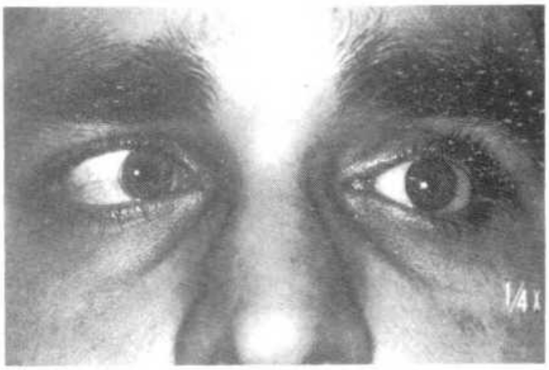

Fig. 1C

from 1 September 1979 to 13 May 1985. These details were used to trace the corresponding medical records. The patients were recalled by letter.

The following details were recorded: enucleation date; patient's age at enucleation; side; reason for enucleation; implant size and type (if inserted).

The patient was then photographed in the primary position, and looking right and left (Figs. 1a, b, c). We looked specifically for laxity of the lower lid.

The artificial eye (AE) was then removed, weighed (to 2 decimal points of a gram), and its volume determined by displacement in a graduated cylinder (to the nearest $0{\cdot}5$ cm^3).

Each patient was subjected to volumetric analysis of their orbits. This was performed as follows. The AE was removed. A drop of oxybuprocaine was instilled into both the good eye and the socket. The patient put on a pair of Speedo swimming goggles which had a 0·25 inch (6 mm) hole drilled through the medial aspect of each of the flat anterior faces (Fig 2). The goggles were adjusted for symmetry on the orbital margins and the patient placed supine. Each chamber of the goggles was filled with normal saline fed from a 20 ml syringe via a narrow cannula (a truncated 21g Butterfly – Fig. 3) and the volume recorded. The fluid was aspirated out through the same cannula, the AE was reinserted, and the patient was thanked and discharged.

Later the photographs were assessed, firstly for an overall impression of cosmetic outcome, and secondly to quantify the excision related abnormalities.

Overall cosmetic assessment was performed as follows. The photographs in the primary position were graded by both an ophthalmologist and a lay person to ensure minimal bias. No grading was given until all the photographs had been seen, so that the extremes of cosmetic variability were known. Each patient was then allocated to one of five groups (scored 1-5 from best to worst) representing the range of cosmetic results which we encountered.

Any abnormalities related to excision were to be measured directly from the photographs and converted to mm. The subjects would then be divided into their cosmetic groups and the results subjected to paired Student's t tests to assess whether any perceived trends were of statistical significance.

Examination of the photographs in dextro- and

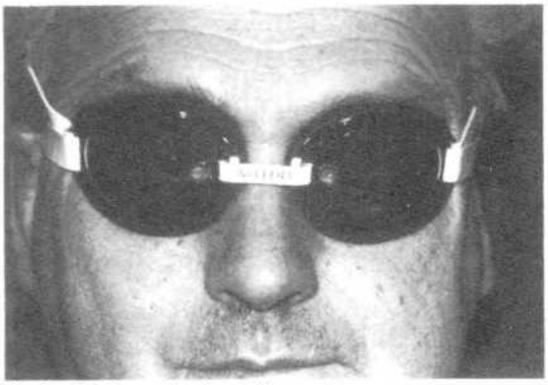

Fig. 2 *The fenestrated goggles.*

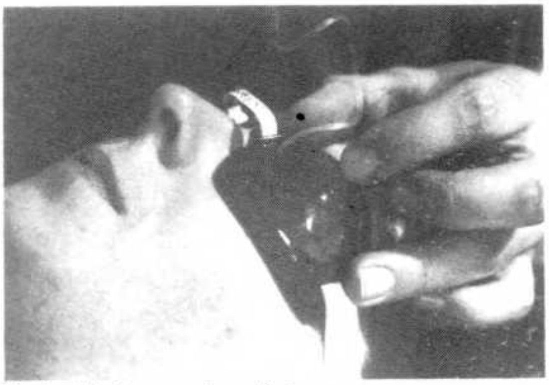

Fig. 3 *The fenestrated goggles in use.*

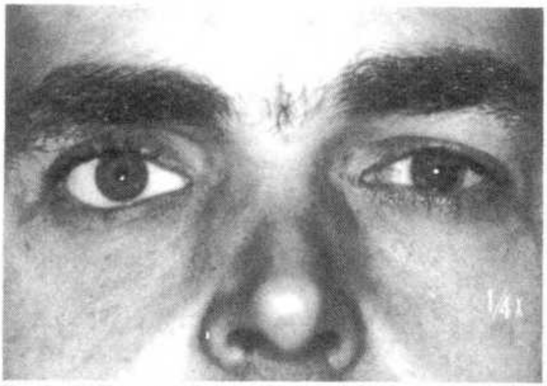

Fig. 4 *Difference in height of palpebral apertures.*

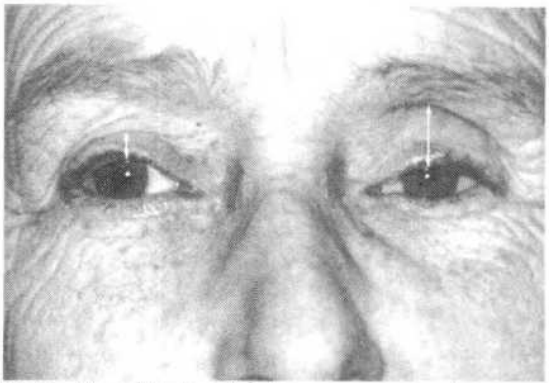

Fig. 5 *Upper lid sulcus showing measurement points.*

laevoversion allowed estimation of the ratio of movement of the eyes. The profile of an AE is such that measurement by the Hirschberg test is highly misleading. We used the change which occurs in the canthus-to-limbus measurement on versions to give a ratio of eye movements. These measurements were taken directly from the photographs.

Results

Over the six-year period 179 eyes were excised. There were 15 eviscerations and 164 enucleations. Eleven records were untraceable. Two patients were known to have died, and 18 others were deemed unsuitable for reasons of health (4), mental state (2), now distant location (12), and not recalled. A total of 148 patients were sent for, but only 56 attended. Four were excluded from analysis, three because of lost photographs and one who refused volumetric measurements. Unfortunately no evisceration patients were included in the analysis.

We recorded a number of abnormalities associated with excision of the eye: orbital volume loss (52, 100%); difference in the height of the palpebral apertures (25, 48%) (Fig. 4); poor movement (52, 100%) (Figs. 1a, b, c); the presence of an upper lid sulcus (51, 98%) (Fig. 5); laxity of the lower lid (36, 69%) (Fig. 6); altered lower lid contour (34, 65%) (Fig. 6); poor centring of the cosmetic shell (36, 69%) (Fig. 7).

There were a number of other features which were AE fitting problems such as: medial edge of the AE visible on abduction (4 cases); poor AE colour match (3 cases); lateral edge of AE visible on adduction (1 case).

The numbers in each cosmetic group are given in column 1 of Table 1.

Orbital volumetric analysis was easy to perform and was not uncomfortable for the patient. Measurements repeated for various reasons were found to vary by less than 1 ml. The averages of the volumetric results are shown against cosmetic grouping in columns 2–5 of Table 1. There was a wide variation in both the enucleated and normal eye volumes (E vol and N vol respectively). The formula (E vol − N vol) gives the orbital volume loss (OVL). If the shell

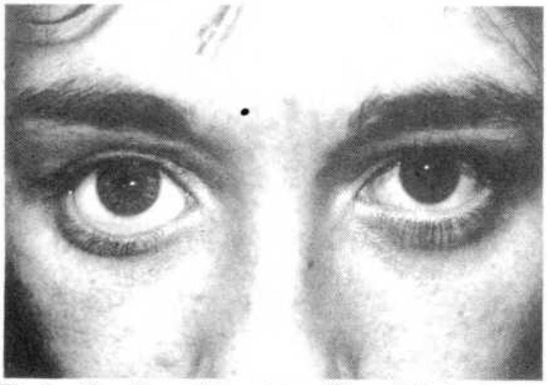

Fig. 6 *Altered lower lid contour and lower lid laxity.*

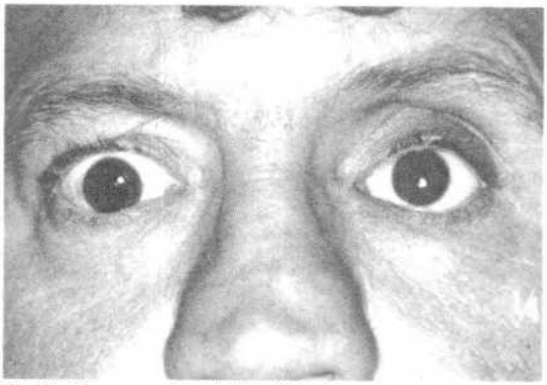

Fig. 7 *Poor centring of the artificial eye.*

Table 1 *Averages of measurements of volumetric analysis, shell weight and volume, palpebral apertures, movement ratio, and lid sulcus against cosmetic group*

Cosmetic group	*n*	*Volumetric analysis*				*Shell*		*Palpebral aperture*			*Movement ratio*	*Lid sulcus*			
		E vol	*N vol*	*OVL*	*OVD*	*Wt*	*Vol*	*N*	*E*	*PAD*		*N*	*E*	*E*	*−N*
Very poor	3	18	12	5	2	3	3	7	8	−1	5 1	3	11	8	p>0 05
Poor	5	15	12	5	1	3	3	9	9	0	3 1	3	8	5	p>0 1
Average	21	19	14	5	3	3	3	9	9	0	4 1	3	6	3	p>0 01
Good	18	18	14	4	2	3	3	10	10	0	2 1	3	5	2	NS
Very good	5	18	15	3	0	3	3	9	9	0	3:1	3	4	1	
	min	9	6	−1	−2	1	1	5	5	−4	1 1.1	0	0	1	
	max	26	19	11	8	5	4	13	14	3	7 7.1	8	14	8	
	mean	19	14	5	2	3	3	9	9	0	3 1	3	6	3	
	SD	3 6	2 5	2 5	2 4	1 0	0 7	1 8	2 1	1 6	1 4 1	2 1	3·2	2 3	

E=enucleated eye N=normal eye OVL=orbital volume loss (E vol–N vol). OVD=orbital volume discrepancy PAD=difference in height of palpebral apertures NS=not significant

volume is added to this figure, ideally there should be a figure of zero. We have termed this the orbital volume discrepancy (OVD). The mean of the orbital volume loss was 6 ml (SD 2·3) in those without an orbital implant and 4 ml (SD 2·5) in those with. The mean of the OVD in each group was 4 ml (SD 2·4) and 2 ml (SD 2·3) respectively

We found that shell volume was broadly related to shell weight, though neither measurement was related to cosmetic result (columns 6 and 7 of Table 1). Those patients without orbital implants (10, 19·2%) had a mean shell weight of 3·1 g (SD 0·9) as compared with 2·8 g (SD 1·1) in those with implants.

There were 25 cases (48%) in which there was a difference in the palpebral aperture of over 1 mm. Neither measurement of the palpebral apertures nor their differences showed any consistent variation with cosmetic group (columns 8-10 of Table 1).

All 52 patients (100%) showed reduction in the ratio of AE movement as compared with the fellow eye (column 11 of Table 1).

In 51 cases (98%) a lid sulcus was demonstrated, and the averaged measurements are shown against cosmetic group in columns 13–15 of table 1. For the purposes of measurement the lid sulcus was taken to be the difference between distances from upper lid margin to first skin crease (Fig. 5). There was a statistically significant correlation between cosmetic group and the extent of the lid sulcus.

There were 36 cases (69%) of lower lid laxity and 34 cases (65%) of altered lower lid contour. These were scored 0–4, from most normal to most abnormal. Averaged scores decreased with better cosmetic groups, though not with statistical significance (columns 2 and 3 of Table 2).

Centring and movement of the AE with respect to the normal eye are also shown in Table 2 (columns 4 and 5). Thirty six patients (69%) had some degree of poor AE centring. Horizontal and vertical centring was scored separately as follows: a score of 0 was given on each scale if the eye was correctly centred. If the AE was slightly decentred, a score of 1 was given

Table 2 *Cosmetic groups against presence of an orbital implant, averages of scores for lower lid laxity, altered lower lid contour, AE centring, and averaged total scores*

Cosmetic group	*n*	*Lower lid*		*AE centring*		*Implant*		*Averaged total scores*	
		Laxity	*Contour*	*Horizontal*	*Vertical*	*Yes*	*No*		
Very poor	3	2 0	1 6	0 6	1 3	1	2	11	p>0 1
Poor	5	1·4	1 4	1 0	1 6	3	2	8	p>0 05
Average	21	1·1	1·1	0 8	1 0	16	5	7	p>0 05
Good	18	1·0	1 0	0 8	0 3	18	0	5	p>0 1
Very good	5	0 4	0 2	0·2	0·2	4	7	2	

Scoring. 0=normal — normal
1=minimal — decentred 4°
2=moderate — decentred 8°
3=marked — decentred 16°
4=very marked — decentred 24°

Table 3 *Age at enucleation and sex distribution against cosmetic result*

Age at enucleation	*Male*	*Female*	*Averaged scores of cosmetic result*
0–19	4	2	1·8
20–39	10	4	2·3
40–59	11	5	2·7
60+	7	9	3·1

Scoring 1=very good 2=good 3=average 4=poor 5=very poor

Table 4 *Reason for enucleation against cosmetic result*

Reason for enucleation	*n*	*Averaged scores of cosmetic result*
Intraocular malignancy	14	3·0
Risk of sympathetic	14	2·5
Blind painful eye	20	2·6
Other	4	2·5

Scoring: 1=very good 2=good 3=average 4=poor 5=very poor

(and the direction of decentring noted). A score of 2 was reserved for more marked decentring. Eighteen (35%) were found to be correctly centred both horizontally and vertically, while 12 (23%) were found to be centred neither horizontally nor vertically. Correct centring was found in 29 (56%) AEs horizontally only and 29 vertically only. Of those AEs with inaccurate centring the common deviations were outwards and upwards. There was no strong correlation between cosmetic group and centring, but there were fewer AEs with both horizontal and vertical deviation in the better cosmetic groups.

We found that the absence of an orbital implant did not necessarily produce a worse cosmetic result, but that in general there was a smaller proportion of subjects without an implant in the better cosmetic groups and vice versa (columns 6 and 7 of table 2).

Table 3 shows the patients by age and sex. There were 32 males and 20 females. In groups of 20 years the figures showed a correlation with cosmetic result, the younger patients tended to show better cosmetic results.

There was no correlation between the reason for excision of the eye against cosmetic group (Table 4). The eyes were excised most commonly for choroidal melanoma and trauma (14 (27%) each).

Finally we divided the subjects into their cosmetic groups and summed all the excision related features apart from movement ratio AE centring, lid laxity, and lid contour were already scored for each subject. Lid sulcus and palpebral aperture measurements were in millimetres and, if added to the scores, would have induced considerable bias. To avoid this, both measurements were scored on a 5 point scale (0-1·5 mm=0, 1·6–3·0 mm=2, 3·1–4·5 mm=3, 4·6–6·0 mm=4, 6·1–7·5 mm=5). A similar scale was used to score orbital volume loss. A statistically significant correlation was found, in that total scores were less in the better cosmetic groups. The results are summarised in column 8 of Table 2.

Discussion

Our first aim was to see if excision related orbital volume loss' could be measured. Orbital volume measurements have been done in the past, but only on skulls.[3,4] In vivo extrapolations have been made from linear measurements from radiographs[3,4] or from CT scanning and image analysis,[4] which, though effective, is still relatively expensive. Exophthalmometry will give the relative positions of the cornea with respect to the orbital margin, but will give only a very rough idea of orbital volume changes. Although our method of measurement is indirect, it is a new, cheap, reproducible, and painless way of measuring orbital volume loss As with exophthalmometry, the absolute figures cannot be used for comparisons between patients, and the test could be misleading in cases of marked facial asymmetry. In an otherwise normal patient the technique was quick and accurate.

As stated, we recorded seven features which were measurable departures from normal structure or function. Of these individual features the upper lid sulcus measurement was the only one to be correlated significantly with overall cosmetic result Upper lid sulcus measurement has been described by Hill and Radford,[7] who measured the anteroposterior depth of the sulcus. We considered that the vertical extent of the sulcus would be more likely to affect cosmetic appearance. Both the presence of lower lid laxity and altered lower lid contour were moderately correlated with cosmetic result, though not with statistical significance. There was no other individual correlation, though, when summed, all the excision related features were correlated with overall cosmetic result.

It has been suggested that many of the excision related abnormalities are linked. To compensate for either ptosis or orbital volume loss a larger artificial eye would be required This heavier artificial eye would, by gravity, press against the supporting lower lid This would lead to some of the other abnormalities such as lower lid laxity and altered lower lid contour.[7] We thought this might in turn lead to the formation of an upper lid sulcus and the centring abnormalities. If this were true, one would expect those factors to be worse with increasing shell weight. This is not borne out by an analysis of the figures. We were unable to demonstrate any other correlations.

There are theories about the aetiology of some of the excision related abnormalities. These were summarised by DeVoe in 1945.[5] The most interesting postulated that the reduction in orbital volume changes the direction of pull of the levator from upwards (round the globe) to backwards, thus producing an upper lid sulcus. If this were true, a direct link would be expected between orbital volume loss and upper lid sulcus. We were unable to demonstrate this. If we had used Hill and Radfords' method of measurement,[7] such a correlation might have been found.

In enucleation with implant it is usual to suture the recti over or through the implant. The obliques are usually ignored. This abolishes their usual forward pull and may add to orbital volume loss and upper lid sulcus. This may account for the anecdotal reports of a better cosmetic result with evisceration where the muscle insertions are not disturbed. We had no evisceration patients in the analysis and so were unable to comment on the cosmetic comparison between the results of enucleation and evisceration.

We have confirmed the fact that after enucleation, in general, an orbital implant is desirable for better cosmetic result and motility. We did not find AE movement as good as has been reported elsewhere,[8 10] but this may be due to differences in measurement techniques. We looked at absolute movement ratios rather than measuring angular deviation of the AE, which we found difficult.

This study tends to confirm that, in general, after enucleation young adults do well and the elderly do badly. We also found that the very young did well in this study, though this was a relatively small group.

In summary, only the upper lid sulcus measurement was correlated significantly with cosmetic result. Other features were of lesser importance individually. Techniques of excision of the eye which do not lead to sulcus formation would seem preferable. Further study is required before a particular method of excision could be recommended.

We were dismayed to find a number of AE fitting problems which we believe should have been avoided. Those who have had to undergo such a procedure should have the benefit of painstaking prosthetic fitting.

We thank the consultant staff at the Birmingham and Midland Eye Hospital for allowing us to investigate their patients We also thank Mr Ivan Bradley, senior medical photographer, for his photographic assistance

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Marginal corneal abscess associated with adult chlamydial ophthalmia

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SUMMARY In four patients with an adult chlamydial ophthalmia small, marginal corneal abscesses were detected. These corneal abscesses were associated with unilateral papillary and follicular conjunctivitis and punctate keratitis. In these patients no bacteria was isolated from the abscesses, but *Chlamydia trachomatis* was isolated from materials collected from the abscesses and from the conjunctival swabbings. In addition all patients had microbiologically proved concomitant chlamydial genital infections. The clinical signs resolved after topical treatment with rifampicin or tetracycline eye ointment for six weeks or systemic treatment with tetracycline for two weeks. Because of concomitant chlamydial genital infection it is advisable to treat patients with adult chlamydial ophthalmia with systemic tetracycline and to refer these patients and their consorts for investigation and treatment of their genital infection.

Adult chlamydial ophthalmia (ACO) of sexually transmitted origin has been reported with increasing frequency.[1] The infection is commonly associated with papillary and follicular responses in the palpebral conjunctiva, fine or coarse epithelial and subepithelial punctate keratitis.[2,3] In this report we present four cases of corneal abscess which developed in association with chlamydial conjunctivitis and in which *Chlamydia trachomatis* was isolated from the abscess material.

Material and methods

CLINICAL EXAMINATION

The patients were referred to the External Eye Diseases Clinic, Moorfields Eye Hospital, London. They were examined by a Haag-Streit slit-lamp, and the severity of symptoms and signs was graded and recorded as described previously.[4]

LABORATORY INVESTIGATIONS

Chlamydial culture. Conjunctival swabbings were collected from all areas of palperbral conjunctiva.[5] Swabbings were also collected from the corneal abscess after the cornea had been washed several times and the epithelium over the abscess removed. Each swab was placed in a plastic vial containing 2SP transport medium[6] with additional fetal bovine serum 3% v/v. The methods of transport and storage of the specimens and methods of culture in irradiated McCoy cells or cycloheximide treated McCoy cells are described elsewhere.[7,8]

Bacterial culture. Swabs for bacterial cultures were collected from the lower fornix of the palpebral conjunctiva, the lid margins, and the corneal abscess separately and plated on blood agar for bacterial culture.

Antibody detection. Blood samples were collected by venepuncture or by sponges following a finger prick.[9] These were tested by a modified micro-immunofluorescence test[10] for the presence and levels of type-specific antichlamydial antibodies.

Results

CASE 1

A 26-year-old married woman presented with a seven-month history of a slightly red and irritable right eye, with a sticky yellowish discharge. During this period she had been treated with chloramphenicol drops 0·5% or neomycin drops 0·5%, and more latterly with prednisolone drops 0·3%, all of which gave temporary relief. For five days she experienced an increasing gritty sensation and severe photophobia.

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The visual acuity in the right eye was 6/12 and in the left 6/6. In the right eye there was a slight ptosis of the upper lid, and the bulbar conjunctiva was mildly chemotic and hyperaemic. The palpebral conjunctiva showed a moderate papillary and follicular hyperplasia. At the limbus an active limbitis with a 1 mm pannus and associated marginal diffuse infiltration were present. The cornea showed some coarse epithelial and subepithelial punctate keratitis near the limbus. At the 6 o'clock position there was a well circumscribed corneal abscess measuring 2 mm× 3 mm involving the epithelium to mid stroma, with a mild stromal oedema surrounding the abscess. No other abnormality was detected in the anterior or posterior segment of the eye. The cornea of the left eye was clear, while the palpebral conjunctiva showed a mild papillary and follicular reaction. Bacterial culture of the abscess material and conjunctiva was negative, whereas a few colonies of *Staphylococcus epidermidis* were isolated from the lid margins. *C. trachomatis* was isolated from the corneal abscess and conjunctiva. Serum IgG antibody against *C. trachomatis* serotypes D to K was present at a level of 1/256. Subsequent genital examination showed a gross cervicitis and a positive chlamydial culture.

The patient recovered fully after two weeks of oral doxycycline with an initial dose of 300 mg followed by 100 mg daily. There was no recurrence of infection during the six months' follow-up.

CASE 2

A man 48 years old had a six-week history of progressive redness, a mucopurulent discharge, and photophobia of the right eye.

The visual acuity in the right eye was 6/9 and in the left eye 6/6. The bulbar conjunctiva of the right eye was mildly hyperaemic, while the palpebral conjunctiva showed severe papillary and follicular hyperplasia mainly in the fornices. The right cornea showed epithelial erosions, and fine and coarse epithelial punctate keratitis mainly in the upper half. The left eye was normal. He was treated with rifampicin eye ointment 1% three times daily for six weeks, with good resolution of clinical signs and symptoms.

Two weeks after completion of the above treatment he returned to the clinic complaining of redness and intense photophobia in the right eye. The bulbar conjunctiva of the eye was moderately hyperaemic, while the palpebral conjunctiva showed a fairly moderate papillary and follicular reaction. There was a little scattered epithelial punctate keratitis mainly in the upper half of the cornea. At the 10 o'clock position a well circumscribed corneal abscess measuring 2·5 mm×1·5 mm was present. A mild stromal oedema surrounded the abscess, with a faint flare in the aqueous. No other abnormality was detected in the anterior and posterior segments of the eye. The left eye was normal. Bacterial culture of the abscess material and conjunctiva was negative, but a few colonies of *Staphylococcus epidermidis* was isolated from the lid margins. *C. trachomatis* was isolated from the corneal abscess and conjunctiva. Serological test showed the presence of IgG antibody against *C. trachomatis* serotypes D to K at a level 1/32.

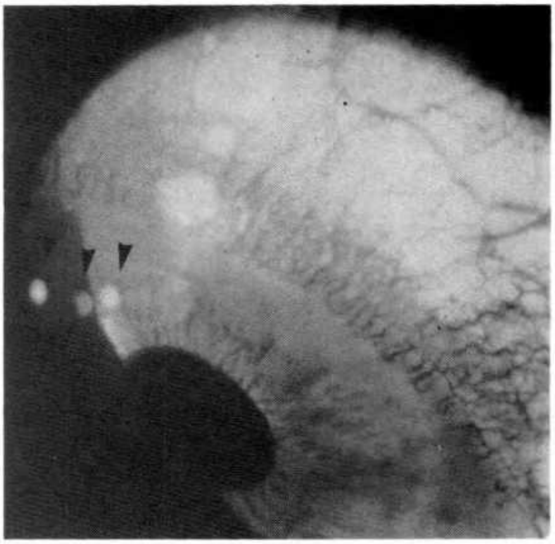

Fig. 1 *Marginal corneal abscesses (arrowed) associated with adult chlamydial ophthalmia (case 3).*

The patient was treated with achromycin eye ointment three times daily for six weeks. Subsequently he was treated with oral tetracycline for two weeks because of a chlamydial genital infection. The patient recovered fully after treatment, and there was no recurrence of infection during the one-year follow-up.

CASE 3

A man 28 years old presented with a three-week history of a red, sticky, and irritable right eye.

The visual acuity was 6/12 in the right eye and 6/6 in the left eye. The lids of the right eye were swollen, there was a tender preauricular and submandibular lymphadenopathy, a mucopurulent discharge, and severely hyperaemic bulbar conjunctiva. The palpebral conjunctiva showed a severe papillary and follicular hyperplasia. The follicles were predominantly in the upper and lower fornices. A few follicles were also present on the plica and caruncle. The limbus was oedematous, with marginal diffuse infiltration and a micropannus. In the cornea three small but discrete and well circumscribed abscesses close to the limbus were present (Fig. 1). The largest was at the 3 o'clock position and measured 2 mm×3 mm, with a mild stromal oedema round it. There were a few folds in the Descemet's membrane and mild flare in the anterior chamber. No other abnormality was detected in the anterior and posterior segments of the eye. The cornea of the left eye was clear, while the palpebral conjunctiva showed a mild papillary and follicular hyperplasia. Bacterial cultures of the abscesses and conjunctiva were all negative. *C. trachomatis* was isolated from the corneal abscesses and conjunctiva. Serum IgG antibody against *C. trachomatis* D to K was detected at a level of 1/128.

The patient was treated with rifampicin eye ointment three times daily for six weeks, which was supplemented with oral tetracycline for two weeks because of a chlamydial genital infection. The patient recovered fully after treatment, and there was no recurrence of infection during the one-year follow-up.

CASE 4

A man 23 years old attended the clinic with a 10-day history of a red, painful, photophobic, and sticky right eye. He also complained of increasing aching in the right ear.

The visual acuity in the right eye was 6/9 and in the left eye 6/5. The right upper lid showed slight ptosis, and the bulbar conjunctiva was moderately hyperaemic. A non-tender right preauricular and submandibular lymphadenopathy was present. The right cornea showed a micropannus, some marginal punctate keratitis, and at the 10 o'clock position a well circumscribed abscess slightly away from the limbus measuring 2 mm×2 mm and surrounded by a very mild stromal oedema. The palpebral conjunctiva showed severe papillary and follicular responses. No other abnormality was detected in the right eye. In the left eye, apart from a mild papillary hyperplasia of the upper tarsal conjunctiva, no other abnormality was present. Bacterial culture of the abscess material was negative, but a few colonies of *Staphylococcus epidermidis* and *Bacillus xerosis* were isolated from the conjunctiva and lid margins. *C. trachomatis* was isolated from the corneal abscess and conjunctiva. Serum IgG antibody against *C. trachomatis* serotypes D to K was detected at a level of 1/256.

The patient was treated with rifampicin eye ointment three times daily for six weeks. He was subsequently treated with oral tetracycline because of a chlamydial genital infection. He recovered fully after treatment, and there was no recurrence of infection during the one-year follow-up.

Discussion

The four cases of ACO reported had developed small marginal abscesses which were associated with a unilateral papillary and follicular conjunctivitis and punctate keratitis. The people specially at risk of developing a corneal ulcer and/or abscess are contact lens wearers, those who have had corneal surgery or trauma or corneal surface disorders, and those with chronic bacterial conjunctivitis.[11] In these cases the corneal abscess tends to be large, and it is generally associated with severe blepharitis, or a contact lens which is not sterilised routinely, or trauma, or corneal surface abnormalities associated with abnormal tear function. Our patients did not belong to any of these risk groups. Bacterial cultures from their corneal abscesses were all negative. *C. trachomatis* was isolated from the abscess material, and all the patients had microbiologically proved concomitant chlamydial ocular and genital infections. It may be argued that the isolation of *C. trachomatis* from the abscess material may have been due to contamination of the corneal specimen with tears containing infectious chlamydial particles shed from the conjunctiva. In order to avoid such contamination we kept the lids apart to prevent blinking, washed the cornea several times, and ruptured the abscess membrane prior to collection of the specimen from the abscess.

The corneal abscesses which developed in our patients were rather small; hence clinically they might be mistaken for subepithelial punctate keratitis (SEPK) or marginal abscess associated with blepharoconjunctivitis. Generally SEPK presents as dull yellow and small opacities (less than 1 mm in diameter) located in the subepithelial and superficial stroma and with no stromal oedema.[3] In contrast the corneal abscesses detected in our patients were dense white lesions located more deeply in the stroma and were surrounded with stromal oedema. The clinical differential diagnosis of chlamydial corneal abscess from bacterial marginal abscess is not feasible; hence it is necessary to rely on chlamydial and bacterial diagnostic tests.

In our patients the corneal abscesses and conjunctivitis responded well to both topical and systemic antichlamydial treatment. However, because of concomitant genital infection we recommend systemic treatment with tetracycline and referral of patients and their consorts for investigation of chlamydial genital infection and necessary treatment.

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Optic nerve involvement in a case of methanol poisoning

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SUMMARY The eyes and optic nerves were studied histologically in a fatal case of methanol poisoning in a 37-year-old man. The most striking findings were bilateral central necrosis of the optic nerves from behind the lamina cribrosa to the orbital apex. Proximal parts of the nerve and the tract showed no necrosis. It is suggested that the complex blood supply of the nerve may be of importance.

Methanol intoxication is a well known cause of blindness in man, the most common observation being oedema of the posterior retina and the optic nerve head. Later optic nerve atrophy develops. The whole sequence of events is thoroughly described by Benton and Calhoun[1] from the Atlanta catasrophe, when 320 persons sought emergency medical care after drinking whisky containing 35% methanol and 15% ethanol. Post-mortem examinations of affected eyes have mainly been concentrated on the retina, where oedema and ganglion cell degeneration have been the main findings.[2,3] However, although optic nerve lesions has been suspected, the optic nerve has only infrequently been investigated.

The object of the present report is to describe a lethal case of methanol poisoning in which optic nerve changes were found.

Case history

The patient, a 42-year-old man, was admitted to the University Hospital in Uppsala after drinking on the previous day a liquor which was later found to contain 80% methanol and no ethanol. On admission he was unconscious and severely acidotic. He had a blood methanol concentration of 114 mmol/l. No ethanol could be detected. The acidosis was corrected within a short time and the methanol concentration diminished by peritoneal dialysis. He was seen by an ophthalmologist on the third day. The pupils were small but reacted to light with a small amplitude. Bilaterally there was slight oedema of the optic nerve heads and of the retinae at the posterior pole. There were no haemorrhages. Computed tomography of the cranium on the same day revealed bilateral necrosis of the putamen regions.[4] The patient developed pneumonia which was resistant to treatment, and, still unconscious, he died on the 20th day after the accident.

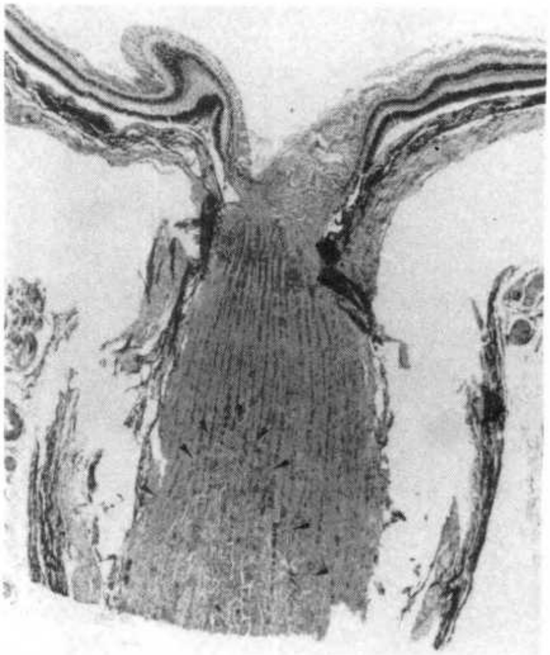

Fig. 1 *Optic nerve head showing the central necrosis ending before the nerve fibres reach the lamina cribrosa (arrows). Luxol fast blue, ×8.*

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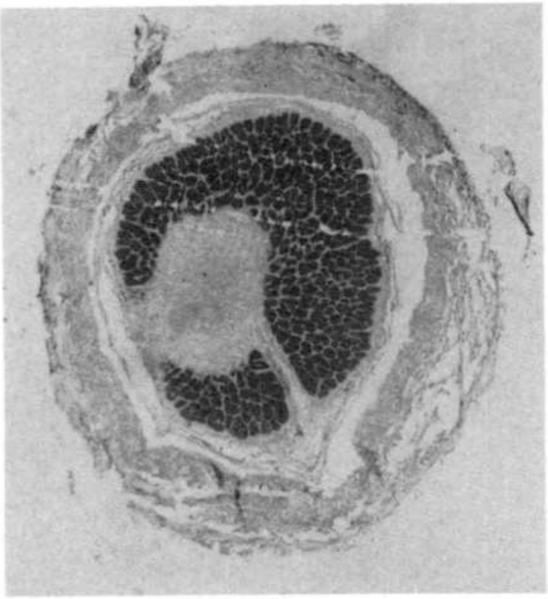

Fig. 2A

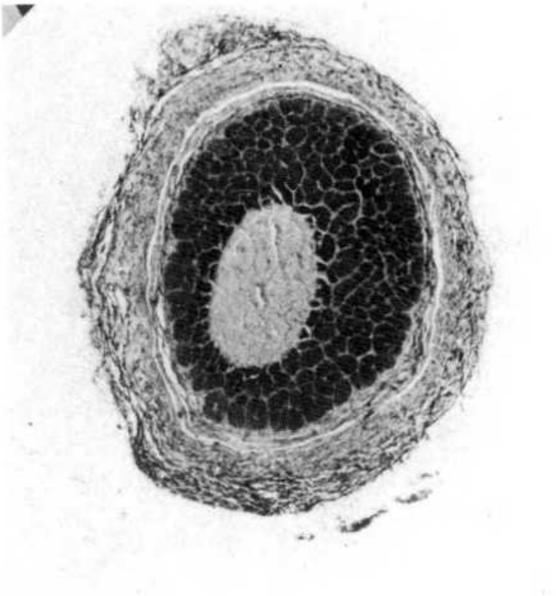

Fig. 2B

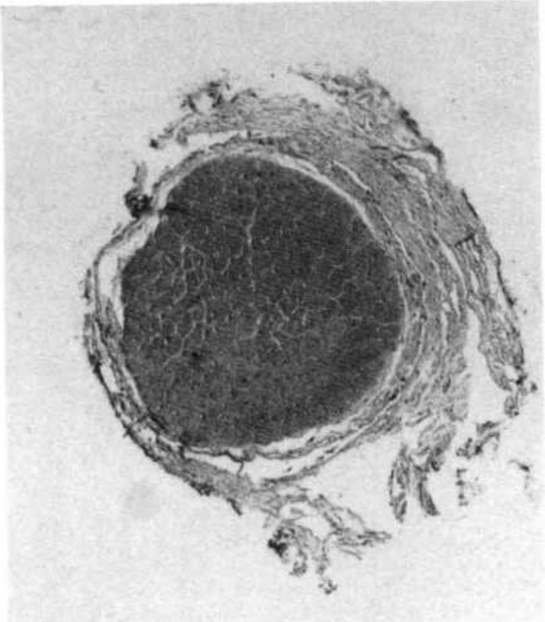

Fig. 2C

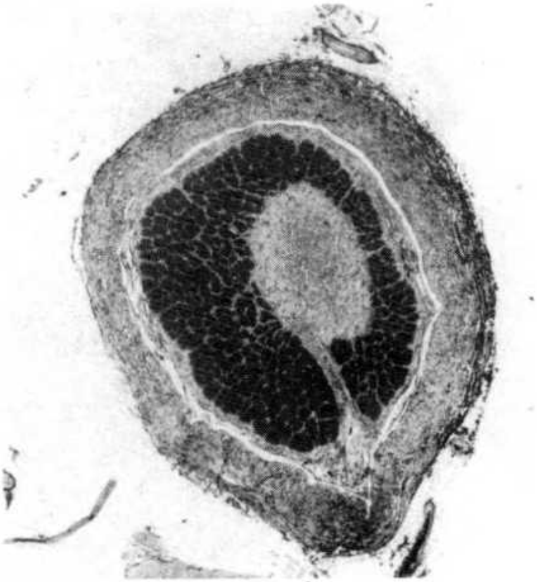

Fig. 2D

Fig. 2 *Cross sections of the right* (A–C) *and left* (D–F) *optic nerve taken 1 cm* (A *and* D) *and 2 cm* (B *and* E) *behind the eye globe and from the apical region* (C *and* F). *The central necrosis is seen in the anterior parts of the nerve* (A–C). A–C: *H and E,* ×7·5, D–F: *luxol fast blue,* ×9.

OCULAR PATHOLOGY

Both eyes with their optic nerves and tracts were investigated after formalin fixation. The eyes were opened horizontally and showed pale, slightly wrinkled retinae without visable haemorrhage. The histological sections from the eye globes displayed no changes in the anterior segment. The optic nerve heads looked normal, but the cut surface of the orbital parts of the optic nerves showed pale central areas. This change was not seen in the optic canal parts of the nerves or in the optic tracts.

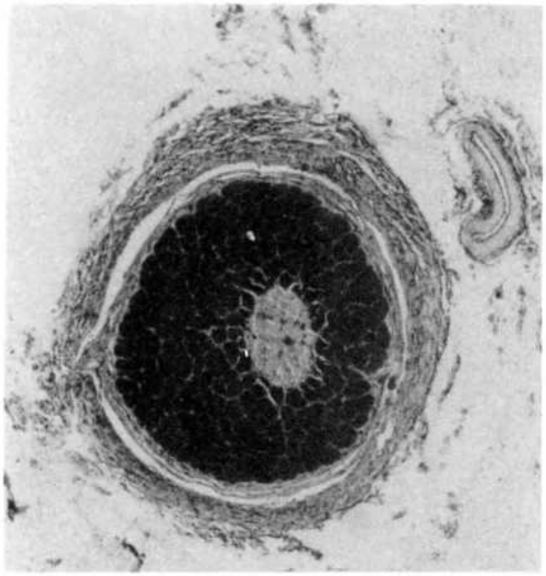

Fig. 2E

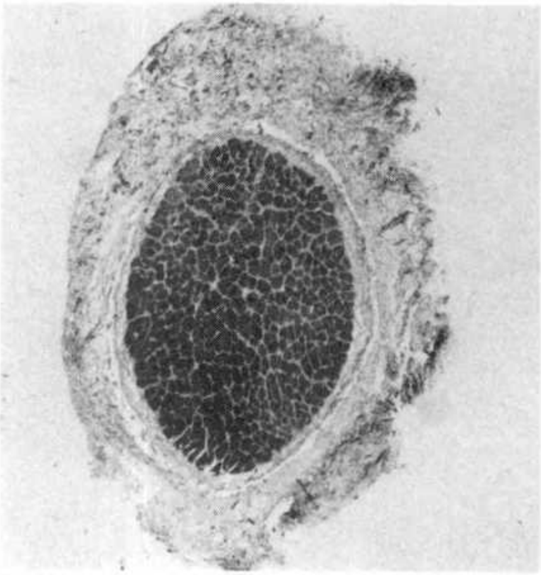

Fig. 2F

Each retina was partly detached by a subretinal serous effusion, and slight retinal oedema was noted. The ganglion cells were slightly enlarged, and in many places the nuclei were laterally displaced. Slight irregularity of the outer and inner nuclear layers and eosinophilic granularity of the plexiform layer were also seen.

The optic nerves showed axonal necrosis in the

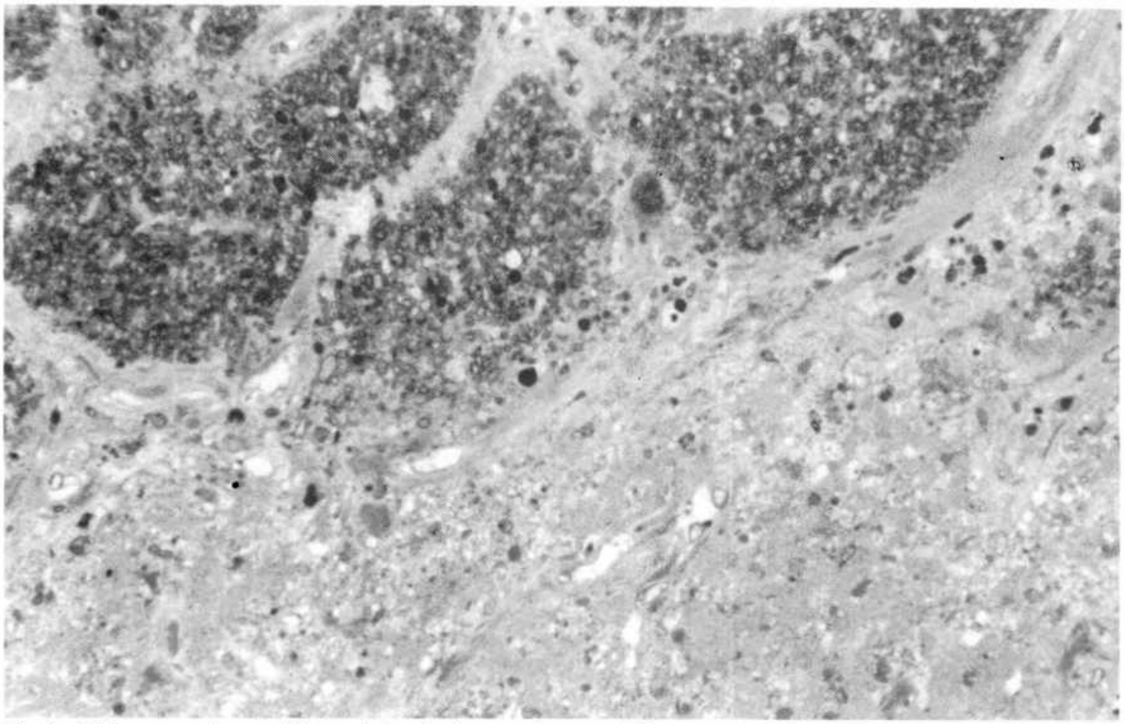

Fig. 3 *High-power micrograph from the border between the necrotic (lower part) and the normally appearing nerve fibres. Note the lack of inflammatory reaction. Toluidine blue, ×430.*

centre, with a sharp border where they met the normally appearing axons in the periphery. The changes extended from 1 mm behind the lamina cribrosa (Fig. 1) to the orbital apex (Figs. 2A–F). There was no inflammatory reaction adjacent to the necrosis (Fig. 3). The lumina of the vessels were open. Myelin staining of the nerve from within the optic canal or from the optic tracts displayed paler staining than normal, possibly due to post-mortem changes. There were, however, no necrotic changes in the nerve proximal to the orbit. The lateral geniculate nucleus appeared normal.

Discussion

The changes in the optic nerves are remarkable. Many authors have speculated about a possible optic nerve lesion but only oedema of the nerve has been reported.[3,5,6] The changes in the retinal ganglion cells have been postulated to be secondary to retrograde degeneration of optic nerve axons and not caused by the methanol intoxication itself.[1,7–9] In recent reports myelin change in the retrolaminal pert of the nerve was observed [10–12] Animal experiments have also shown optic nerve involvement. Birch-Hirschfeld[13] described myelin degeneration in a rabbit two weeks after methanol poisoning. Signs of axonal necrosis combined with venous congestion and oedema were seen in apes by Pick and Bielschowsky[5] after 2–3 weeks. In an experiment with rabbits Fanta and Mayer-Oberditsch[14] found only optic nerve oedema.

The selective bilateral damage of the orbital part of the optic nerve is difficult to understand. In the cases reported the changes started 1–2 mm behind the lamina cribrosa and involved the orbital part of the nerve only. The blood supply may be of importance. The immediate postlaminar part is abundantly supplied by the short posterior ciliary artery. The orbital part is supplied by the pial plexus, with branches from the ophthalmic artery extending perpendicularly into the nerve, providing a generous perfusion especially of the nerves at the periphery.[15] This may to some extent explain why the central part of the nerve is more vulnerable. The perfusion of the central parts of the nerve from a central optic nerve vessel with different extension may be of importance.[16,17] The central infarctions suggest a collapse of the capillary bed, as has been suggested for similar changes in a case of bilateral ischaemic optic neuropathy.[18]

The skilful technical assistance of Margareta Bjorling is gratefully acknowledged

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Haemangiopericytoma of the lacrimal sac: a case report

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SUMMARY A primary haemangiopericytoma of the lacrimal sac in a 45-year-old male is reported. The neoplasm, highly unusual in this location, recurred twice before being correctly identified. Total excision with surrounding tissue appears to be the treatment of choice for this tumour, the behaviour of which is often unpredictable.

After the concept of haemangiopericytoma as a tumour of pericytes was introduced by Stout and Murray in 1942,[1] its occurrence has been reported in many parts of the body, most often in the head and neck.[2] In the ophthalmic literature we find it reported mainly in the orbit as single case reports or as clinicopathological studies of larger series.[3] To our knowledge only one case has been previously observed in the lacrimal sac.[4]

Case report

The patient, a 45-year-old male, traced his clinical history back to when he was 40. Then he began complaining of a progressively increasing right eye epiphora which led after about six months to a dacryocystorhinostomy. The patient remained free of symptoms for several months, after which the epiphora recurred and a mass appeared below the right medial canthus. The mass was for some time reducible, as if due to dilatation of the lacrimal sac; later on it acquired the clinical features of a slowly growing neoplasm. Surgical intervention 24 months after dacryocystorhinostomy revealed a tumour involving the entire lacrimal sac. It was then histologically diagnosed as a 'benign cellular schwannoma'. The neoplasm recurred one year later, necessitating a second operation. A further recurrence became apparent seven months later, at which time the patient was sent to our clinic for consultation.

Physical examination revealed a firm, non-mobile subcutaneous mass bulging below the right medial canthus (Fig. 1). The mass was painless, and the overlying skin, not involved by the tumour, was hyperthermic by 2°C when compared with the opposite site. The CT scan showed a solid tumour with well defined contours occupying the bone defect left by the previous dacryocystorhinostomy. The tumour projected into the nasolacrimal duct, which was markedly dilated (Fig. 2). At surgery the tumour appeared under the medial palpebral ligament as a well circumscribed mass, surrounded by dense connective tissue and engaged in the nasolacrimal duct. After sectioning of the ligament the tumour was removed together with the surrounding tissue and the mucosa of the nasolacrimal duct. Infiltrating areas

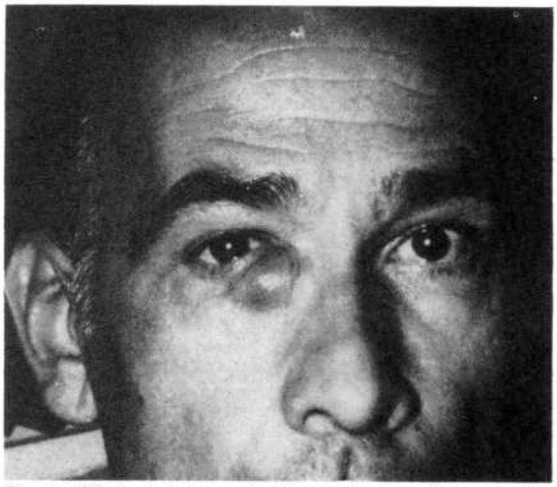

Fig. 1 *Clinical photograph taken at the time of the second recurrence, showing the tumour mass bulging just below the right medial canthus.*

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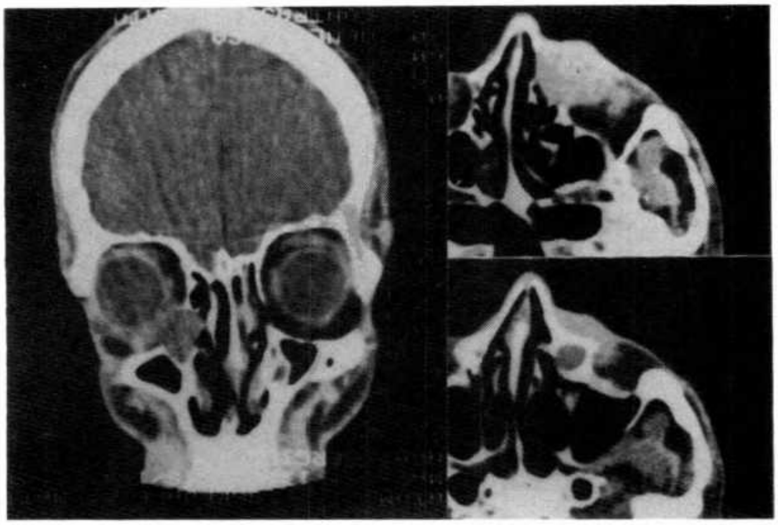

Fig. 2 *Coronal (left) and axial CT scan (top right) show the tumour filling the bone defect, but no destruction of the bony margins. On lower axial scan (bottom right) the enlarged nasolacrimal canal is seen (compare with the opposite canal on the same scan).*

were not found, and the tumour mass could be easily removed in toto.

On its cut surface the neoplastic tissue was firm, greyish-white, and homogeneous, with a slightly multinodular texture. Microscopically the tumour showed a prominent vascular pattern, best appreciated with reticulin stain, with tightly packed oval or spindle shaped cells growing haphazardly around thin-walled vascular channels (Figs. 3, 4). The tumour cells were uniform, with plump nuclei, ill-defined cytoplasmic borders, and a moderate degree of anaplasia (Fig. 5). Scattered areas were highly cellular, with four to five mitotic figures in 10 high-power fields. A fibrous capsule surrounded the entire neoplasm. Neither haemorrhage nor necrosis was observed, nor was vascular or capsular invasion. The immunohistochemical stain for S-100 protein was negative throughout the tumour tissue. The factor-VII-related antigen was present only in the endothelial cells lining the vascular spaces.

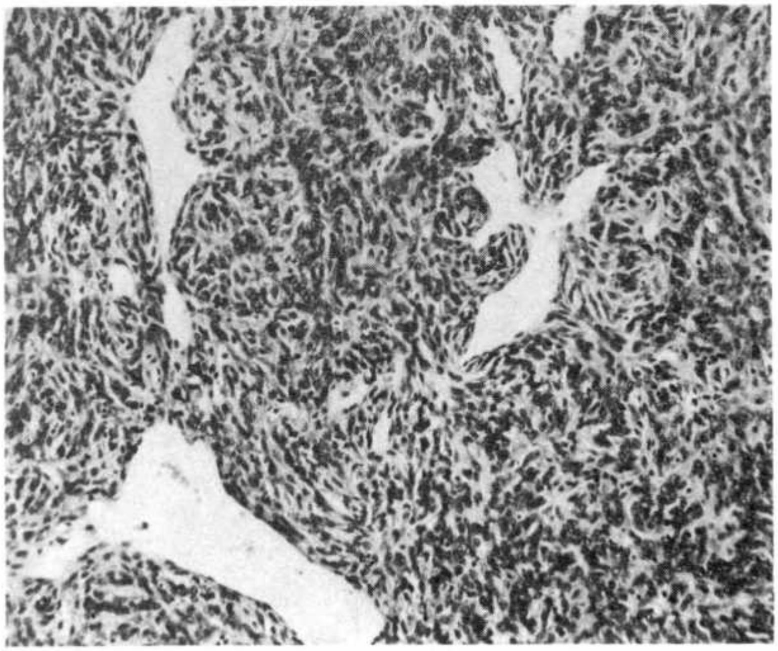

Fig. 3 *The tumour cells proliferate around and between thin walled vessels and vascular spaces lined by a flattened endothelium. H and E, ×100.*

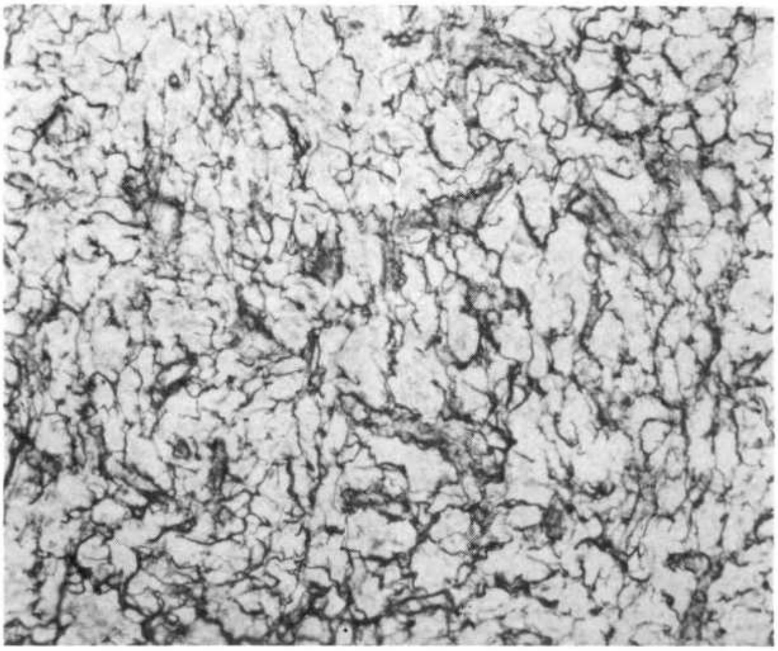

Fig. 4 *Reticulin stain outlining the vascular structures ramifying throughout the tumour tissue, and the reticulin meshwork between the proliferating cells peripheral to the vascular channels. Gomori's method, ×100.*

Because of the morphological and immunohistochemical findings the diagnosis of haemangiopericytoma was suggested. We subsequently had the opportunity to review the slides of the previous histological examinations: the haemangiopericytomatous pattern was already present, though somewhat inconspicuous, since the vascular spaces were compressed and obscured by the proliferating cells. Compared with the previous slides the present morphology showed an increased cellularity of the neoplasm, with higher mitotic index and an increase in the degree of cellular anaplasia.

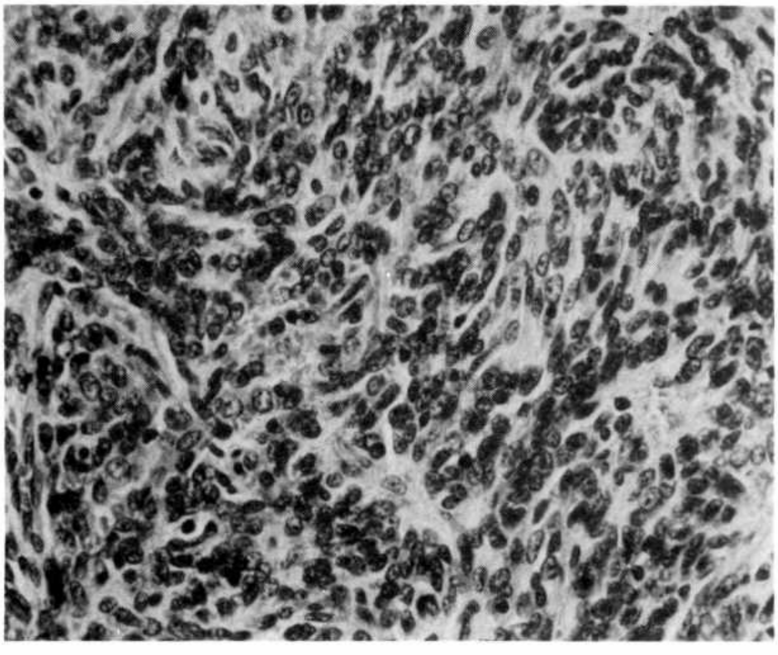

Fig. 5 *In the most cellular areas the tumour cells have uniform larger nuclei, are in a disorderly arrangement, and compress the vascular channels. H and E, ×200.*

The postoperative course was uneventful and the patient was dismissed without any further therapy. Three and a half years after the last operation he was alive and free from signs of recurrence or metastasis to distant sites.

Discussion

Haemangiopericytoma is an uncommon neoplasm, and knowledge of its clinical manifestations, biological behaviour, and treatment derives largely from cases affecting soft tissues. Its histological identification and differentiation from imitators rests entirely on adequate sampling from various areas of the tumour to demonstrate the uniform cell population and the uniform histological appearance. In the present case previous consultants had interpreted the lesion as a benign cellular schwannoma. We rejected this interpretation on the grounds of both the morphological and the immunohistochemical findings in the recurring tumour. Further, the thermographic findings gave a possible clue to the nature of the tumour, indicating its high vascularity

The morphological distinction, or grading, of haemangiopericytomas in terms of their malignant potential is difficult and somewhat controversial. Some authors maintain that accurate grading is possible and useful,[2,5] while others have presented evidence that the assessment of the malignant potential from morphological features is not reliable.[6] This was also the experience of Croxatto and Font[3] in their series of orbital tumours, where recurrences and metastases developed in cases classified benign or borderline.

In our case not all the morphological signs of malignancy were present, while the clinical history clearly indicated an aggressive behaviour, with recurrences within a short span of time. The first clinical symptoms, as in most lacrimal sac tumours, appeared long before the tumour growth became evident, mimicking a chronic dacryocystitis or a post inflammatory stenosis of the lacrimal tract, thus leading to a delay in correct diagnosis and appropriate therapy. But in our case both the clinical history and the morphology of the lesion, which changed on successive histological examinations, suggest that the neoplasm may have been benign at first, becoming malignant only later in its natural history. Such a course has also been observed by Massarelli *et al.*[7] in a haemangiopericytoma of the parotid gland. It is also reported, however, that a borderline malignant appearance may not significantly change over a span of many years.[8]

A wide total incision of the tumour, whenever possible, appears to be the treatment of choice. The efficacy of radiotherapy and chemotherapy is not established at present. If removal is incomplete, recurrences are almost the rule. The local recurrence rate for this tumour varies from 17 to 80% and is dependent also on the site of the lesion: in the orbit it approaches 30%.[2] However, long follow-up periods are mandatory, as the tumour may recur as long as 20 or more years after the initial surgical treatment.

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Primary Ewing's sarcoma of the orbit presenting with visual loss

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SUMMARY A case of primary Ewing's sarcoma of the orbit and paranasal sinuses in a 6-yearold boy is reported. The child presented with headaches and unilateral visual loss. Loss of vision as a result of optic nerve involvement with primary Ewing's sarcoma is extremely rare.

Ewing's sarcoma is a malignant small round-cell tumour typically occurring in the first and second decades of life[1] and classically involving the long bones of the limbs, the ribs, or the pelvis.[2-4] Primary Ewing's sarcoma of the head and neck region is unusual and generally involves the mandible or maxilla.[5] We describe a case involving the orbit and paranasal sinuses in a child with a long history of headache and apparently normal initial findings, who ultimately developed visual loss as a result of optic nerve involvement with primary Ewing's sarcoma.

Case report

A 6-year-old boy was referred to the Hospital for Sick Children, Toronto, for investigation of headaches and visual loss. His symptoms had started six months previously with a right frontal headache that lasted three days. The headache then recurred every few weeks, lasting up to two hours each time. He was examined on several occasions by his general practitioner, but no abnormality was found. There had been no history of vomiting, nasal obstruction or discharge, systemic symptoms, weight loss, or visual problems at that time. A plain radiograph of the skull taken shortly after the onset of the headaches was reported as normal (Fig. 1A).

Seven days before admission the boy complained of a severe headache and said that his vision was 'going black' in the right eye. Profound visual loss was present in that eye. Repeat plain skull films demonstrated widening of the superior orbital fissure, disruption of the medial third of the sphenoidal ridge, destruction of the planum sphenoidale, and opacification of the right ethmoid sinus (Fig. 1B). The patient was referred to this centre for further examination and management.

On admission, the child was alert, co-operative, and in no distress. Vision in the right eye was limited to bare perception of light temporally. In the left eye the visual acuity was 6/6 and the visual field was full on Goldmann perimetry. There was 2 mm of right axial proptosis measured with the Hertel exophthalmometer. External examination was otherwise normal. No periorbital masses were palpable round the eye. Ocular motility was unremarkable except for a slight limitation of abduction on the right. The pupils were equal, round, and reactive, but there was a 4+ right relative afferent pupillary defect. Examination of the right fundus revealed a swollen, elevated optic disc with venous engorgement and some loss of the nerve fibre layer. The left fundus was normal.

A computed tomography (CT) scan (Figs. 2A, 2B) showed a large, uncalcified, hyperdense soft-tissue mass involving both ethmoid sinuses, the sphenoid sinus, and the right orbit. The tumour eroded through the planum sphenoidale and the roof of the right orbit, extending superiorly and posteriorly into the anterior and middle cranial fossae. The medial and lateral walls of the right orbit were involved posteriorly, so that the proximal portion of the optic nerve could not be delineated from tumour. More anteriorly there was lateral displacement of the optic nerve and medial rectus muscle associated with extensive destruction of the medial wall of the orbit The left orbit appeared uninvolved. The tumour showed homogeneous contrast enhancement, with a generally well-defined border in the portion extending intracranially, suggesting that it was extradural.

General examination, ear, nose, and throat exami-

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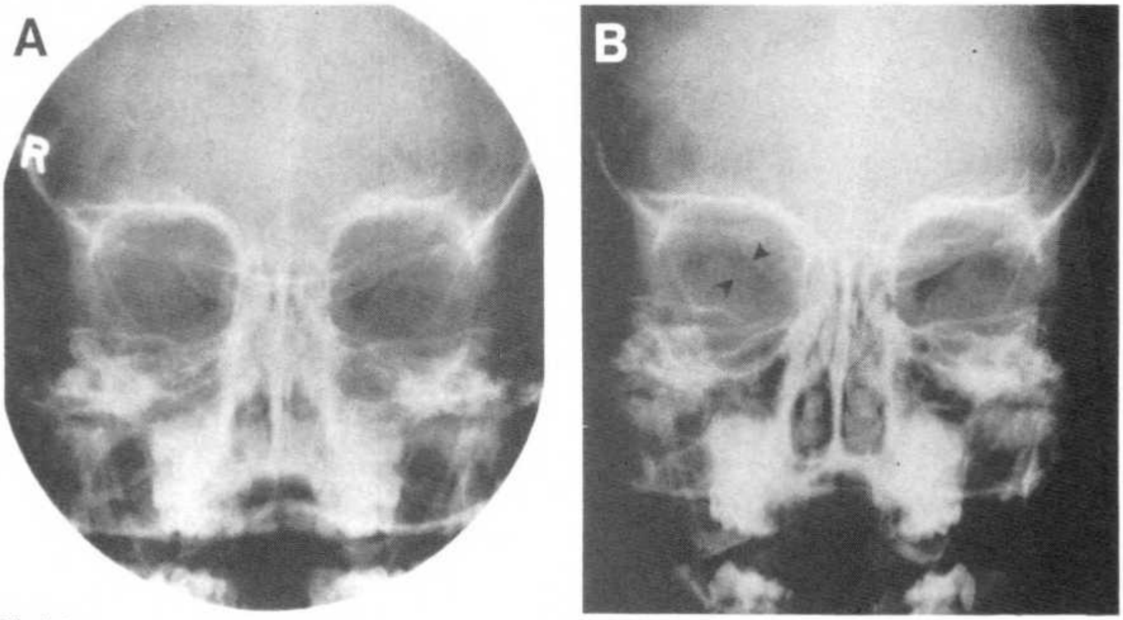

Fig. 1A

Fig. 1B

Fig. 1 *Plain radiographs of the skull.* A: *Six months before admission.* B: *At the time of admission for investigation of right visual loss. Note widening of the right superior orbital fissure (arrows).*

nation, and neurological assessment were normal. An investigation for metastases, which included bone and gallium scans, a liver-spleen scan, a CT scan of the chest, bone marrow biopsy and aspiration, and examination of cerebrospinal fluid cells failed to demonstrate any other lesion.

An ethmoidectomy and biopsy of tissue from the sphenoid sinus performed under general anaesthesia demonstrated Ewing's sarcoma.

COURSE

After surgery the child underwent a course of radiation and chemotherapy. 50 Gy targeted to the right orbit and surrounding areas of tumour involvement were administered in 25 fractions, with shielding of the left eye. The patient was prescribed intravenous vincristine, cyclophosphamide, and actinomycin D as a seven-day course once a month. One dose of cytosine arabinoside, methotrexate, and hydrocortisone was given intrathecally. Six weeks after treatment was started a CT scan showed dramatic shrinkage of the soft-tissue tumour. A CT scan seven months after starting treatment showed healing of the lytic bony lesions, with no recurrence of the tumour mass (Figs. 2C, D).

Nine months after diagnosis the patient continued to receive chemotherapy. He was well and free of headaches. In his right eye there was no light perception and marked optic disc pallor had developed. Visual acuity, visual field, and fundus appearance in the left eye remained normal.

HISTOPATHOLOGY

Tissue for light microscopy was fixed in 10% buffered formalin, processed routinely, and embedded in paraffin. Sections were stained with haematoxylin and eosin (H and E) and periodic acid Schiff (PAS), with and without diastase pretreatment. For immunohistochemistry, sections were stained by the peroxidase-antiperoxidase (PAP) technique using desmin (Euro Diagnostics, Apeldoorn, Netherlands), myoglobin (Miles Scientific, Naperville, Illinois), actin (Dr S. Huang, Sunnybrook Medical Centre, Toronto), S-100 protein (Dakopatts, Glostrup, Denmark), vimentin (BioGenex, Dublin California), neurofilament (Euro Diagnostics), and common leucocyte antigen (Dako).

Tissue for electron microscopy was fixed in 1% glutaraldehyde and 4% paraformaldehyde and embedded in Epon-Araldite. Sections were stained with uranyl acetate and lead citrate.

LIGHT MICROSCOPY

Large clusters and sheets of tumour cells infiltrated bony and soft tissues of the biopsy specimen (Fig. 3A). Tumour cells had uniform round to oval nuclei with dispersed chromatin and occasional nucleoli (Fig. 3B). These cells had a scanty to moderate

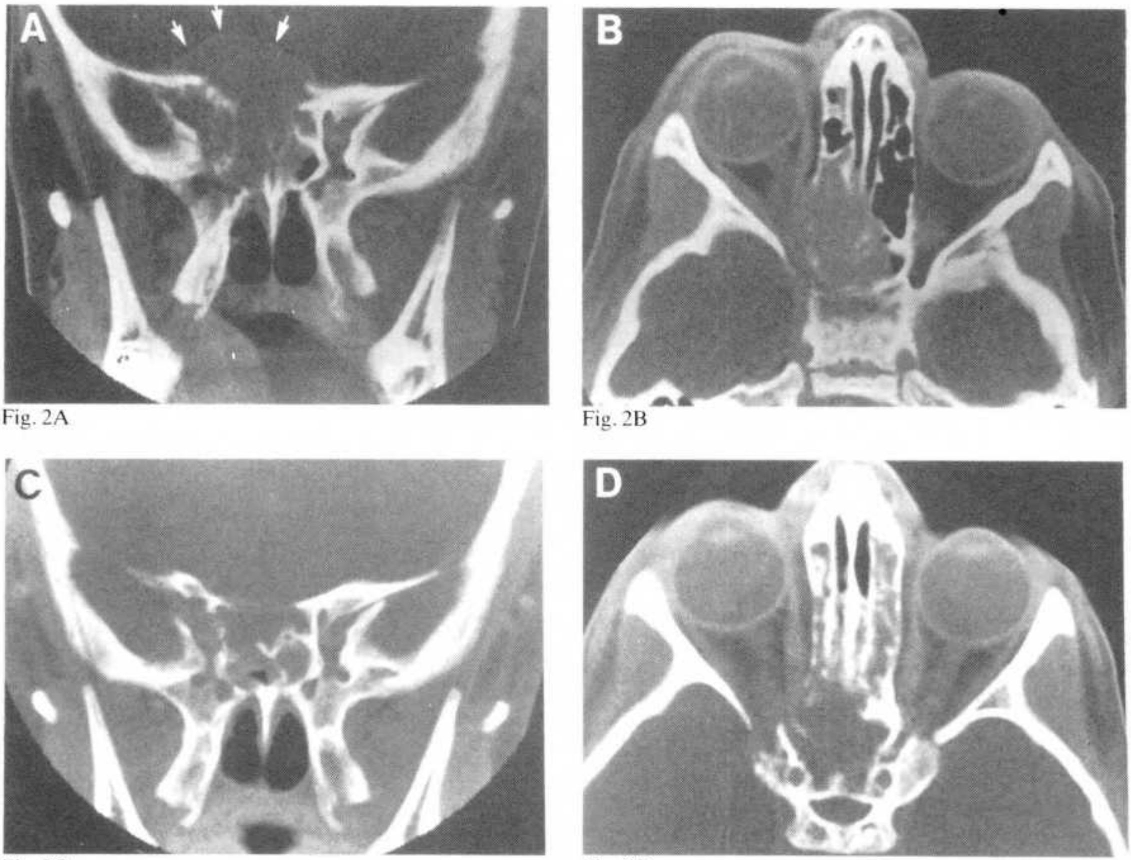

Fig. 2A

Fig. 2B

Fig. 2C

Fig. 2D

Fig. 2 *Coronal and axial CT scans of the orbits. A, B: At the time of admission for investigation of right visual loss. Note the well-defined superior border of the tumour (arrows).* C, D: *Seven months after starting treatment. Note the resolution of the tumour, with substantial healing of the lytic bony lesions.*

amount of vacuolated cytoplasm, which stained for PAS-positive diastase-labile material, indicating the presence of glycogen (Fig. 3C). No evidence of rosette formation or rhabdomyoblastic differentiation was seen.

IMMUNOHISTOCHEMISTRY

Antibody staining was positive for vimentin only (Fig. 3D). Staining for desmin, myoglobin, and actin (skeletal muscle markers), for neurofilaments, S-100 protein and neuron-specific enolase (neural markers), and for common leucocyte antigen (a lymphoid tissue marker) was negative.

ELECTRON MICROSCOPY

On electron microscopy the tumour cell nuclei contained clumped chromatin at their periphery and a rare nucleolus. The cells possessed a moderate amount of cytoplasm, in which large lakes of glycogen were prominent (Figs. 4A, B). The cytoplasm was relatively simple, with occasional mitochondria and numerous free ribosomes. Occasional tight junctions were identified between tumour cells (Fig. 4C). There was no evidence of neurosecretory granules or neurofilaments. Cytoplasmic processes

Fig 3 A: *Photomicrograph of ethmoid bone showing infiltration of marrow spaces by a tumour composed of small round cells. Edges of bony trabeculae show scalloping indicative of resorption.* (H and E, ×138). B: *Higher magnification of the tumour showing a uniform sheet of small cells with round, bland nuclei and small amounts of clear cytoplasm.* (H and E, ×553). C: *tumour cells stained for glycogen, showing abundant deposits within the cytoplasm (arrowheads). (PAS with haematoxylin, ×553).* D: *Tumour cells stained for vimentin by immunoperoxidase technique, showing perinuclear staining: nuclear counterstain has been omitted. (Immunoperoxidase, ×553.)*

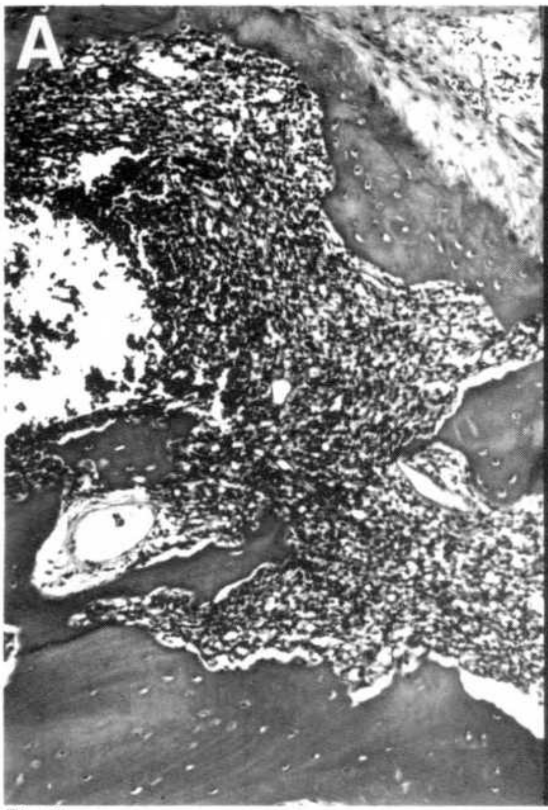

Fig. 3A

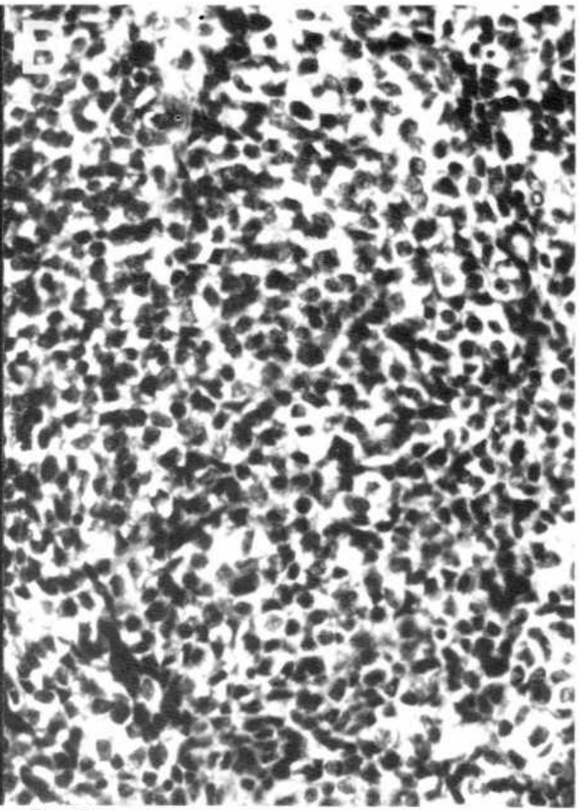

Fig. 3B

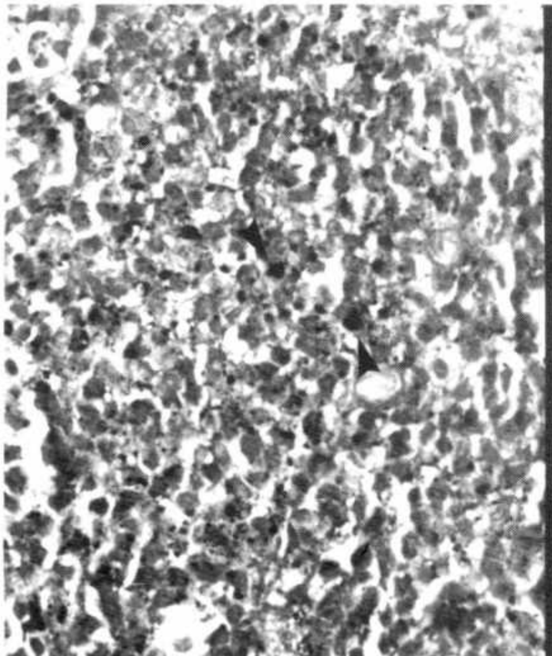

Fig. 3C

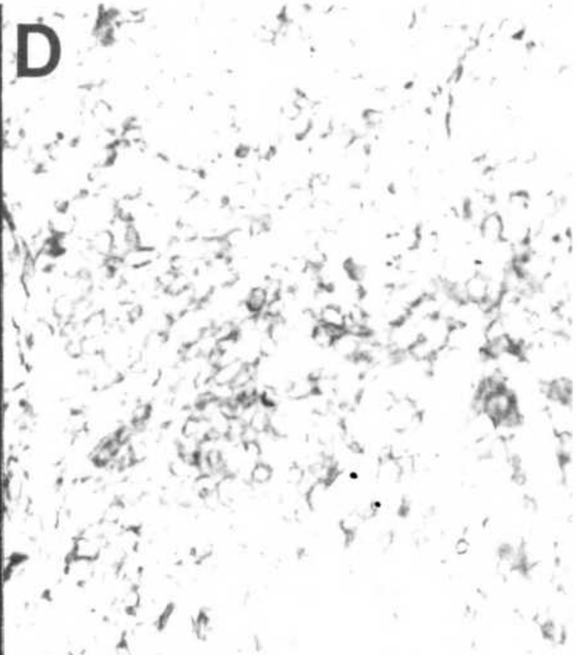

Fig. 3D

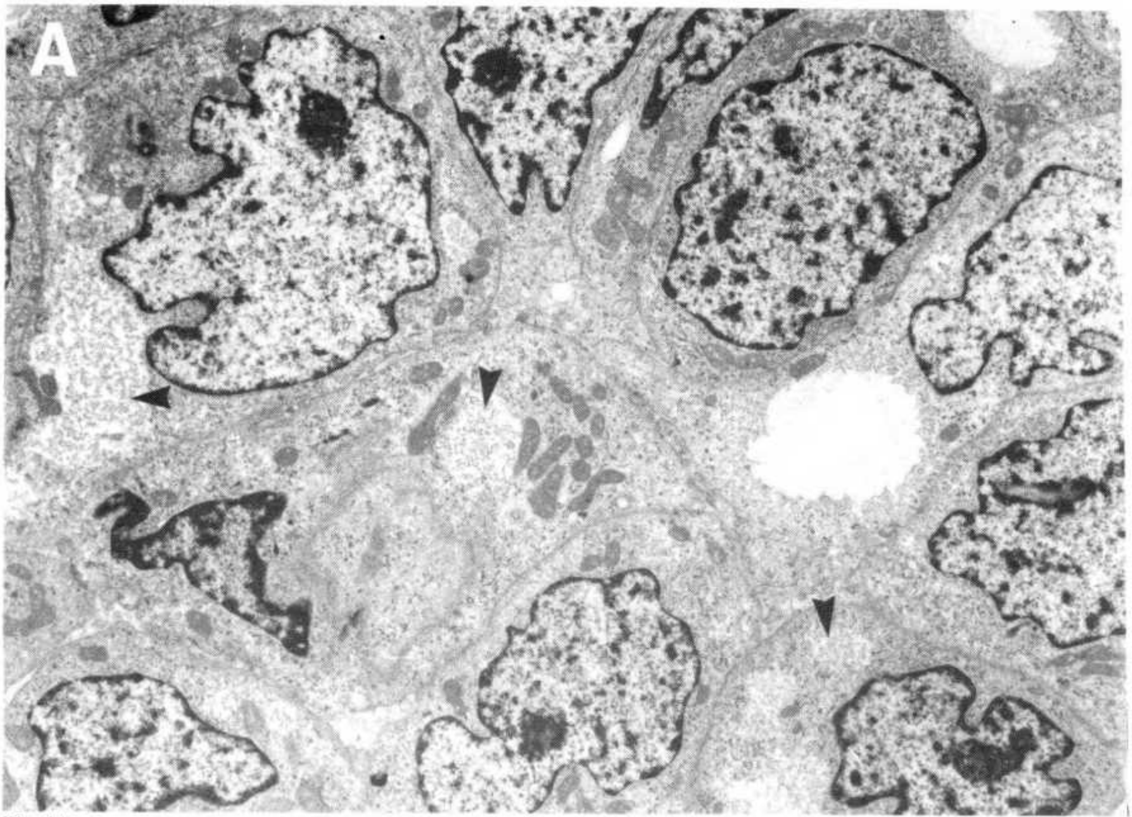

Fig. 4A

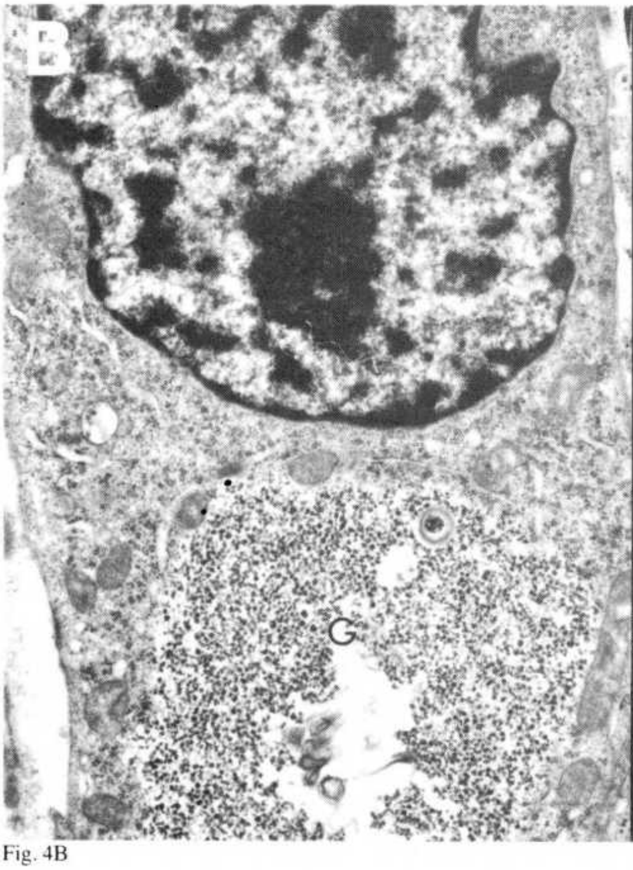

Fig. 4B

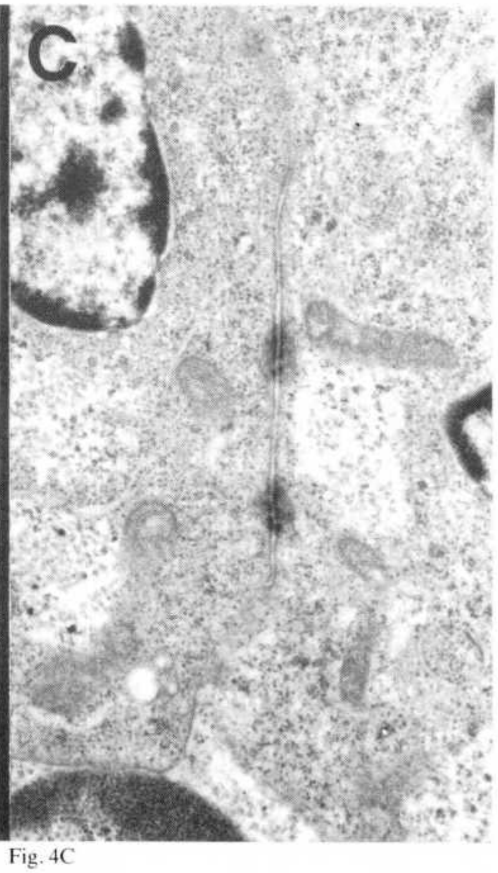

Fig. 4C

were poorly developed. There were no thick or thin filaments, and no Z-band material was seen.

Discussion

The history of rapid visual loss, together with optic disc swelling and a small degree of proptosis, in a patient in this age group suggested the possibility of an orbital tumour such as rhabdomyosarcoma. The CT appearance suggested that the large, soft-tissue tumour could be biopsied by infracture of the inferior turbinate, notwithstanding the intact nasal mucosa and clinically normal ENT examination.

Histologically a small round-cell tumour was found. Based on light microscopy, the differential diagnosis at this patient's age included rhabdomyosarcoma, lymphoma, neuroblastoma, and Ewing's sarcoma. Light, immunohistochemical, and electron microscopy demonstrated characteristic features of Ewing's sarcoma, including relatively simple cytoplasm with few intracytoplasmic organelles, the presence of intracytoplasmic glycogen, occasional tight junctions, and positive staining for vimentin Cell markers and ultrastructural features of neural, skeletal, and lymphoid tumours were absent. The thorough search for another primary site was negative, confirming that the tumour was a primary Ewing's sarcoma of the right orbit and paranasal sinuses.

Orbital Ewing's sarcomas are usually metastases from distant sites.[6 7] In Coley and colleagues[1] review of 91 patients with primary Ewing's sarcoma seen over a 30-year period there was no patient with a primary tumour in the head and neck. More recently primary tumours in this region have been recognised as accounting for 2–3% of all Ewing's sarcomas, with most of these affecting the mandible.[5 8] The previously reported cases of primary Ewing's sarcoma arising in the orbital region have presented with a visible exostosis[9] or a massive intracranial tumour[10 11] or both.[12 13]

Harbert and Tabor[13] described a 19-year-old man who presented with temporal fossa swelling, gross proptosis, and diplopia, but minimal impairment of vision. His massive tumour originating in the temporal fossa was demonstrated histologically to be Ewing's sarcoma, and it proved fatal within a few months despite radiotherapy. Yamada and Takahashi[10] described the post-mortem pathology of a patient with a large intra- and extracranial primary Ewing's sarcoma that involved the orbital region. Alvarez-Berdecia *et al.*[12] reported on a 6-year-old boy who presented with headaches and a rapidly growing tender exostosis on his forehead. He had papilloedema associated with a massive intracranial tumour arising from the supraorbital region and occupying most of the anterior cranial fossa. Vision in the eye was 20/50 (6/15). Beraud and Fortin[11] described two cases of Ewing's sarcoma with intracranial extension and papilloedema but apparently no direct involvement of the optic nerve. Both of these patients died within three weeks of presenting with a bony swelling in the temporal region. More recently Howard and Lund[9] reported on a patient who presented with an exostosis palpable over the nasal bridge and apparently normal visual function; he had a primary Ewing's sarcoma of the ethmoid sinus.

Our patient's presentation differed substantially from those described previously in the literature. This boy had no externally visible lesion and minimal proptosis. His principal complaints were headache and profound visual loss. To the best of our knowledge this is the first case of a primary Ewing's sarcoma presenting with substantial visual loss.

Small round-cell tumours of the orbital region producing visual loss are not rare in the first and second decades of life,[4-14] but typically they are lymphomas or rhabdomyosarcomas. When poorly differentiated they can be distinguished from Ewing's sarcoma only by immunohistochemical and electron-microscopic techniques that have become widely available only relatively recently. Thus previous surveys of orbital and paranasal tumours may have included some unrecognised Ewing's sarcomas. If this is the case, primary Ewing's sarcoma of this region, including cases with visual loss, may be recognised more frequently in future.

Fig. 4 A: *Electron micrograph showing tumour composed of cells with round to slightly convoluted nuclei, occasional nucleoli, and occasional cytoplasmic organelles, mainly mitochondria and free ribosomes. Large glycogen lakes (arrowheads) are prominent* (×7000) B. *Higher power of a single tumour cell showing cytoplasmic glycogen deposits* (G) (×10 500.) C: *Portions of two tumour cells showing occasional cell junction formations* (×14 875)

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British Journal of Ophthalmology, 1988, **72**, 793–795

Ocular involvement in sinus histiocytosis with massive lymphadenopathy

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SUMMARY Sinus histiocytosis with massive lymphadenopathy is a distinct clinical entity, with ophthalmic involvement in 10% of patients. Orbital as well as eyelid lesions have been described as part of the extra-lymph node involvement of this disorder. We recently examined a young boy with sinus histiocytosis with a bulbar conjunctival mass and chronic dacryocystitis.

Sinus histiocytosis with massive lymphadenopathy (SHML) is a disease of childhood and adolescence of unknown aetiology.[1 2] It affects blacks more often than whites and has a self-limited course. The manifestations of sinus histiocytosis include lymphadenopathy with fever, leucocytosis, anaemia, raised erythrocyte sedimentation rate (ESR), and hypergammaglobulinaemia.[3 4] Ocular lesions have been described in the orbit, eyelids, and uveal tract.[5 6]

We report a case of sinus histiocytosis with involvement of the conjunctiva and lower lid of the left eye and bilateral chronic dacryocystitis.

Case report

A 15-year-old black male from Honduras, small for his age, presented with non-tender, non-fixed submental and axillary lymphadenopathy, and an upper lobe opacity in the left lung. The right leg and scrotum had painless, non-pitting oedema with dry skin and soft, non-tender cutaneous nodules (Fig. 1). The testes were small.

The best corrected visual acuities were 20/20, and intraocular pressures were normal in both eyes. Both lacrimal sacs were distended, and pressure over them resulted in a reflux of a yellowish purulent discharge. A 10×8 mm nodule was present on the medial aspect of the left lower eyelid. This lesion was not tender, freely moveable, and was not related to the lacrimal drainage apparatus. On the medial aspect of the left bulbar conjunctiva an isolated, 5×5 mm, oval, pinkish nodule, partly covered with prominent blood

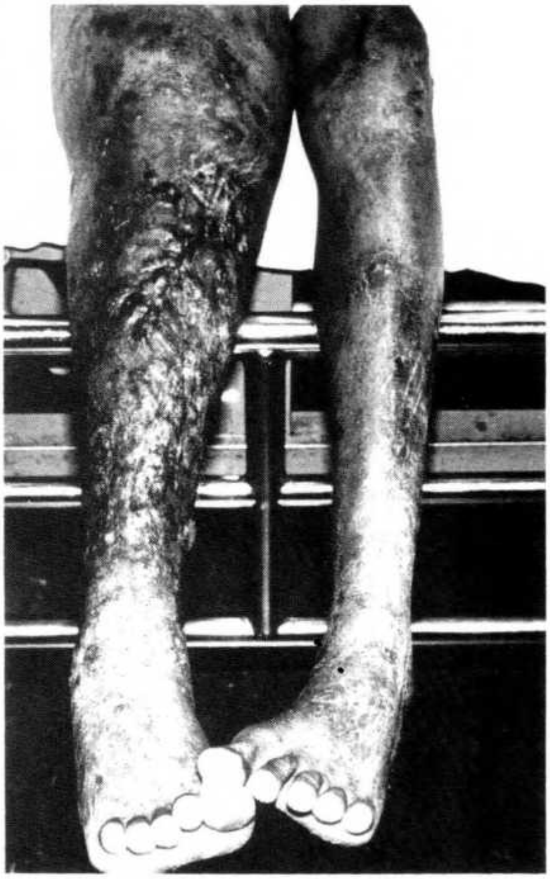

Fig. 1 *The right leg with marked oedema and cutaneous nodules, particularly located in the lower leg.*

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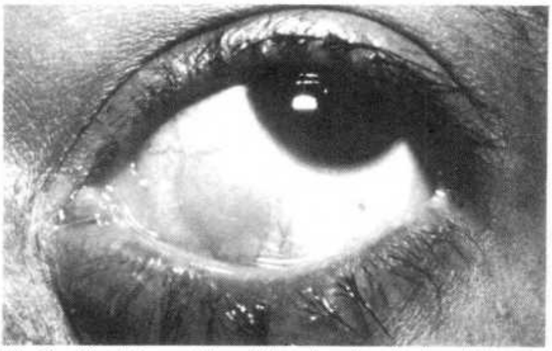

Fig. 2 *The left eye with eyelid and conjunctival nodules.*

vessels was observed (Fig. 2). This nodule was fixed to the underlying sclera. The neuro-ophthalmological and funduscopic examinations were within normal limits.

Laboratory and radiological examinations to rule out an infectious cause and/or some tropical disease related to the lymphadenopathy gave negative results. The ESR was 71 mm/h. The patient was severely anaemic with a packed cell volume (haematocrit) of 26·7%. The results of immunological investigation were consistent with primary immune deficiency. A CT scan of the orbits and sinuses revealed a left ethmoidal mass.

The lymph node biopsy from the left axillary region showed reactive lymphoid hyperplasia with distended sinuses containing a mixed population of cells including histiocytes, lymphocytes, plasma cells, and red cells. The predominating cell type, however, in the sinuses and in the medulla was histiocytes. Additional tissues obtained from the conjunctival nodule and ethmoidal sinus showed the same histology of a mixed infiltrate composed of histiocytes, lymphocytes with occasional plasma cells, and polymorphonuclear leucocytes. The predominating cell type in these biopsies was also the histiocyte, showing great morphological variation and phagocytic properties. These cells were large and irregularly shaped, with abundant, sometimes vacuolated cytoplasms and one or several oval nuclei and prominent nucleoli. The cytoplasmic vacuoles contained phagocytosed red cells, lymphocytes, and irregular proteinaceous deposits which were presumed to be cellular debris (Fig. 3). Mitotic figures were very rare. Immunoperoxidase stain for epithelial membrane antigen (EMA) was negative.

Lacrimal probing was performed and silicone tubes were placed into the nasolacrimal drainage system bilaterally. This procedure, in addition to systemic antibiotic treatment, resulted in a marked improvement of the dacryocystitis. The patient's general condition improved in four months with symptomatic support, and he left the hospital to return to his native country.

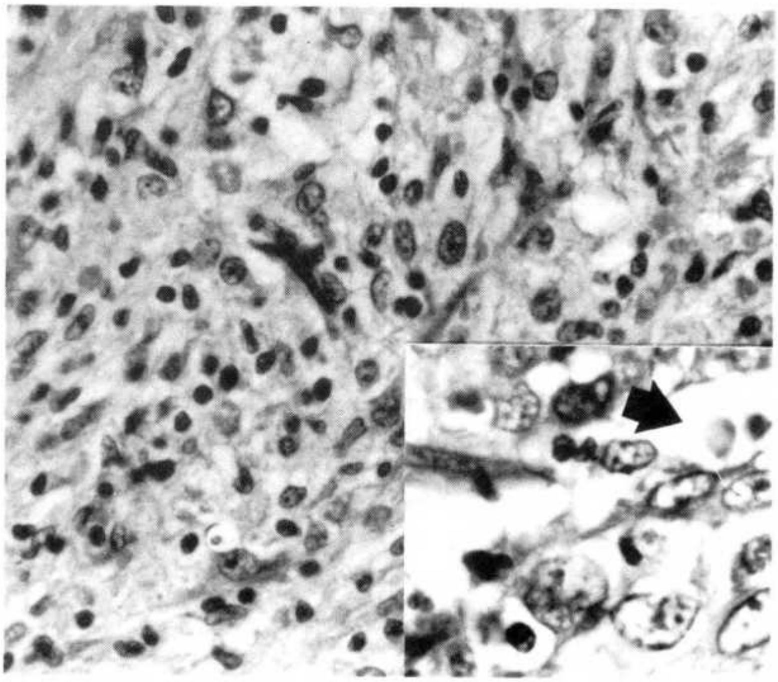

Fig. 3 *The histological appearance of the conjunctival nodule with histiocytic infiltrate. The cells have vesicular nuclei with prominent nucleoli and abundant eosinophilic cytoplasm. Phagocytosed red cell fragments and proteinaceous deposits are identified in some hystiocytes (arrow). H and E; main photograph×250; inset×1000.*

Discussion

Sinus histiocytosis is generally a benign, non-neoplastic condition characterised by massive lymphadenopathy. Cervical adenopathy is most common, with axillary, inguinal, and mediastinal lymphadenopathy not infrequent. Approximately 10% of reported cases have ophthalmological involvement, generally limited to the orbit and eyelids.[6,7]

Berger and associates[8] observed keratic precipitates in a young girl during a routine eye examination. The patient also had a raised intraocular pressure which appeared to fluctuate according to the status of her systemic disease. Friendly *et al.*[7] described four cases with orbital involvement and ocular complications. One patient developed endophthalmitis necessitating enucleation, and in another patient a subconjunctival mass in the medial central region extending into the orbit was excised.

Our case illustrates that the conjunctiva and nasolacrimal drainage system can also be affected in sinus histiocytosis with massive lymphadenopathy as part of the disease's extranodal involvement.[6] The chronic dacryocystitis was most probably due to involvement of the nasal mucosa by sinus histiocytosis spreading round the inferior nasolacrimal drainage system, resulting in obstruction. Nasolacrimal tubes improved the chronic dacryocystitis, and the other ocular lesions regressed. Only a long-term follow-up can determine the final outcome of the disease process.

The cause of sinus histiocytosis is obscure. The condition is considered to be a primary immunodeficiency of histiocytes or of infectious aetiology Sinus histiocytosis should be differentiated from Burkitt's lymphoma and other malignancies as well as from histiocytosis X, which is totally unrelated. The histopathological features of the disease are a result of remodelling of the lymph nodes, which is similar in extranodal sites as well as in the lymph node itself.

Epithelial membrane antigen (EMA) denotes a group of glycoproteins which are present in epithelial cells and appears to act as a marker of proliferation in some epithelial and non-epithelial cells. EMA positivity has been reported in certain types of histiocytic proliferations.[9,10] To explore this phenomenon, immunoperoxidase stains for EMA were performed on multiple sections in our case, but failed to reveal significant EMA positivity.

Therapy is not specific. Some cases respond to local excision, systemic immunosuppression, or radiation.

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The 'poor man's' Landers lens

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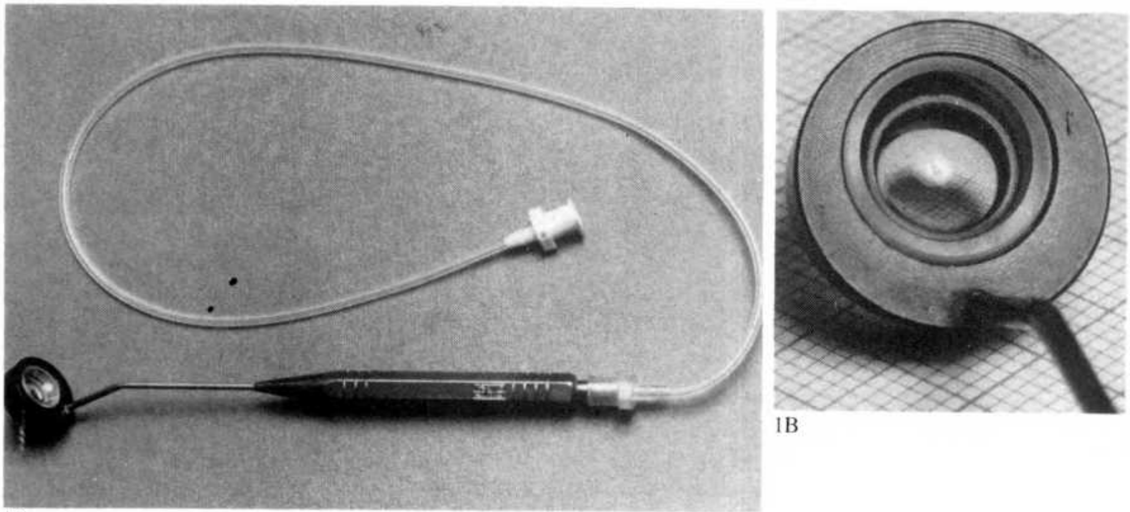
SUMMARY A clinical application of the technique of 'autoindirect ophthalmoscopy' in a gas-filled, phakic eye is described. Peroperative photographs obtained by this technique are demonstrated and the optics described.

Recently an interesting observation[1] was made of a real, aerial, inverted image anterior to the cornea in a gas filled phakic eye. The final comment in that article alluded to the clinical usefulness of the phenomenon. This paper describes its use at vitrectomy.

Vitrectomy is often accompanied by gas exchange to treat posterior-pole lesions and tamponade bleeding points. The timing of the fluid-gas exchange varies with the procedure, but it is often necessary to visualise the retina through the gas for endophotocoagulation, 'fluting' of subretinal fluid, and a variety of other therapeutic procedures. In this unit a biconcave, irrigated contact lens (90 dioptres) is generally used to obtain a right-way-round image of the retina for these procedures, the Landers lens[2] (Figs. 1A, B, 2A, B).

Occasionally the view through such a lens is so distorted that the lens is removed, the operating microscope elevated about 2 cm, and an indirect view of the retina is obtained (Figs. 3A, B). This image can be utilised for further therapeutic manoeuvres (the 'poor man's Landers lens'). The technique varies from that described by Thaller[1] because the source of illumination at vitrectomy is often the intraocular fibreoptic. As described,[1] the cornea/aqueous/lens complex acts as +100 dioptres condensing lens while there is gas in the vitreous cavity (as compared with +58·64 dioptres in a normal eye), forming an image I at distance V from its nodal point N_1 (Fig. 4).

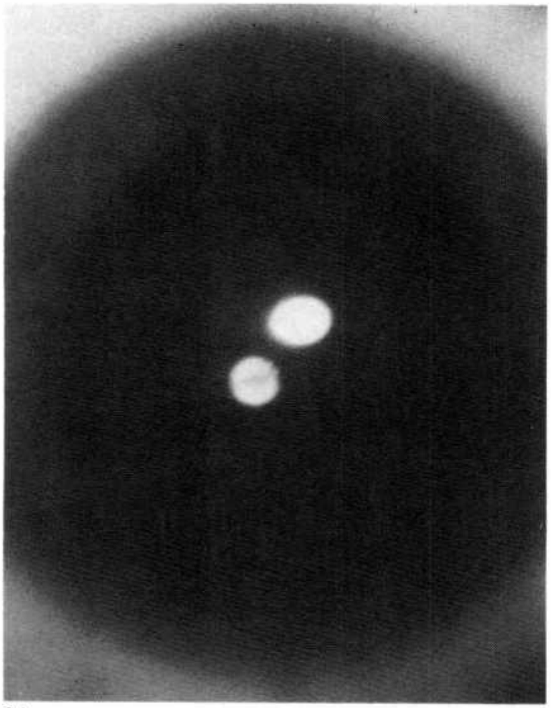
Correspondence to Larry Benjamin, FRCS, Oxford Eye Hospital, Woodstock Road, Oxford.



1A

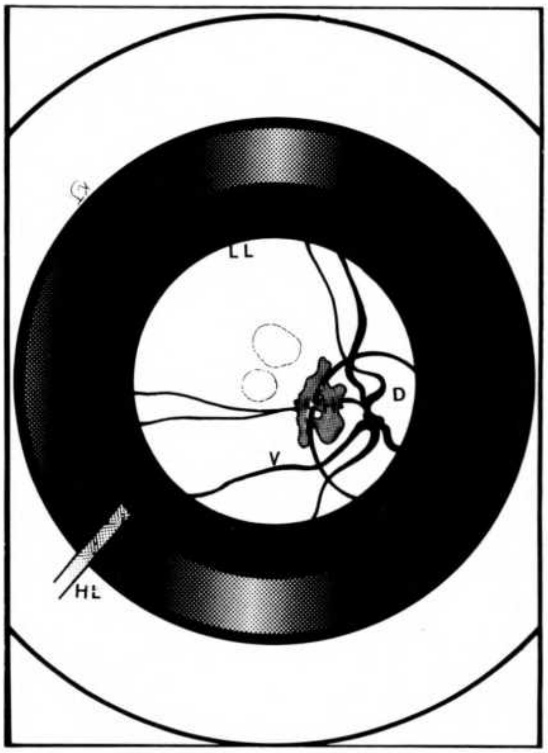
1B

Fig. 1A, B *The Landers lens: a biconcave irrigated contact lens.*



2A

Fig. 2 A: *Photograph of retinal image formed through Landers lens.* B: *Optic disc* (D), *haemorrhage overlying disc* (H), *and vessels* (V). *Also shown are the edge of the lens* (LL) *and its handle* (HL).



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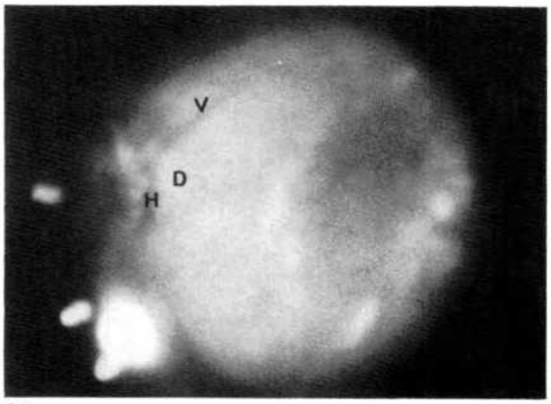
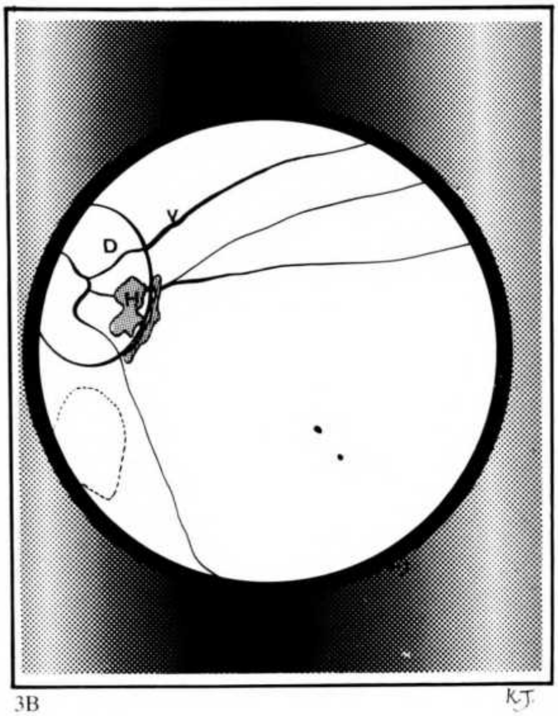
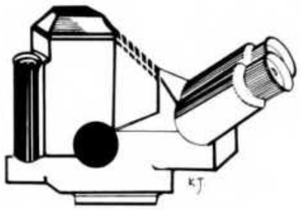


3A

Fig. 3 A: *Photograph of retinal image as formed by the method shown in Fig. 4.* B: *Optic disc* (D), *haemorrhage overlying disc* (H), *and vessels* (V). *Note the image inversion as compared with Fig. 2.*



3B



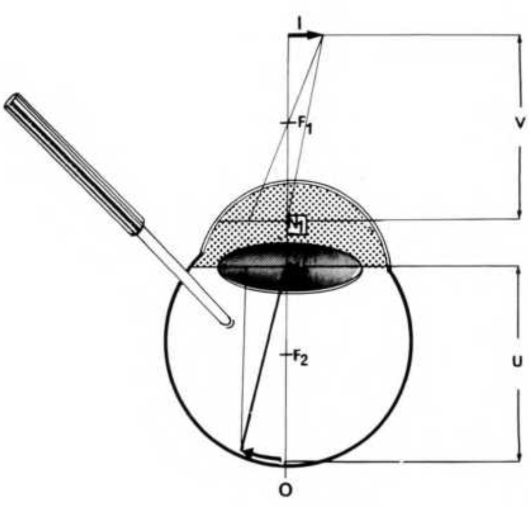


Fig. 4. *Diagram to show formation of the retinal image in a gas filled phakic eye utilising endoillumination. The 'lens/aqueous/cornea' complex acts as a 100-dioptre converging lens for light rays coming from the gas filled vitreous cavity. I=image. O=object. U=object distance. V=image distance.* N_1 *and* N_2*=image and object nodel points respectively.*

In keeping with the theoretical optics described, for myopic eyes the microscope needs to be elevated less than for emmetropic ones. This fact relates to the object distance U being greater in longer, myopic eyes. In fact, the microscope's coaxial light can be used to obtain an image as described by Thaller,[1] but owing to bright 'Purkinje image' reflections its use is limited. However, in the performance of very anterior peripheral endophotocoagulation—for example, just postorally—even this method is occasionally used.

The quality of the pictures obtained suffers from the long exposure times necessary, especially when using light from inside the eye. The image produced by the photo slit-lamp benefits from flash source exposure. The view obtained at surgery is adequate owing to the 'variable film speed' of the surgeon's retina.

The observation that indirect funduscopy can be performed with a gas filled phakic eye does have clinical and therapeutic application.

I thank Mr David McLeod, FRCS, for his encouragement.

References

1 Thaller VT. Indirect funduscopy in a gas-filled eye: an observation. *Br J Ophthalmol* 1986; **70:** 155–6.
2 Landers MB, Stefansson E, Wolbarsht ML. The optics of vitreous surgery. *Am J Ophthalmol* 1981; **91:** 611–4.

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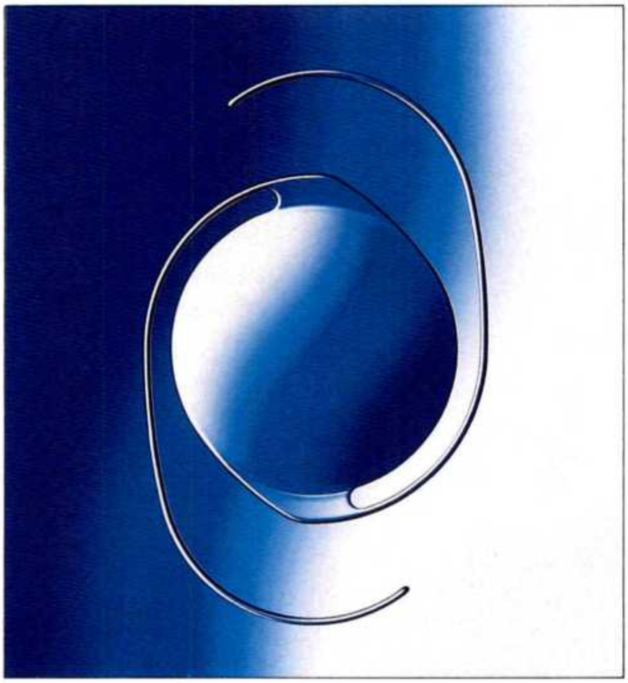

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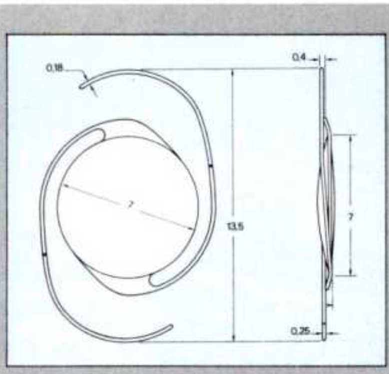

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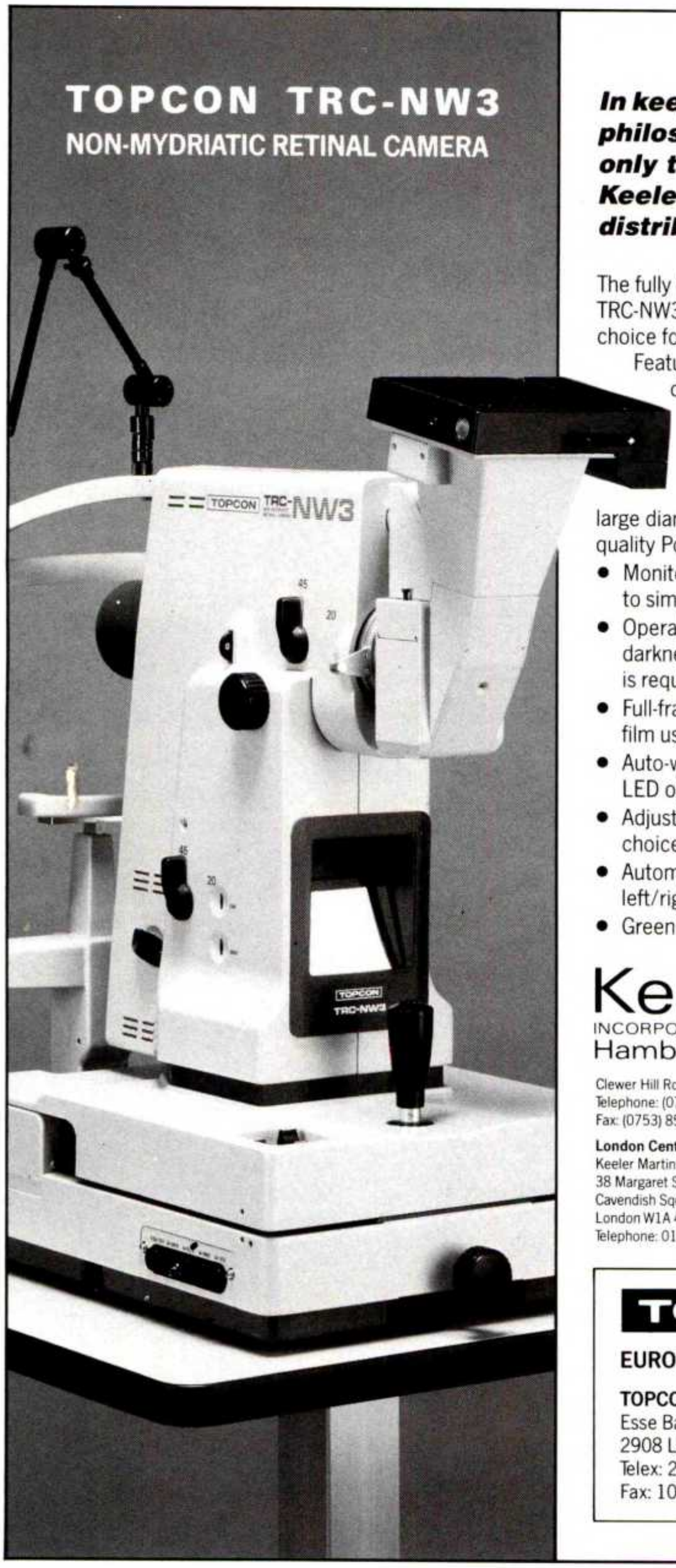

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Book reviews

Contemporary Issues in Ophthalmology: Open-Angle Glaucoma. By GEORGE W WEINSTEIN. Pp. 275. £40·00. Churchill Livingstone: Edinburgh. 1986.

This book is a collection of 13 chapters, all from different North American authors. As is so often the case with publications from multiple authors the contributions vary considerably in quality. Some are fully referenced reviews, others more anecdotal, and in such a brief text there can only be patchy coverage of the subject. The beginner will therefore find it useful as a supplement to one of the basic texts on glaucoma.

Some of the chapters are more valuable than others, and those on diurnal variation in intraocular pressure, signs of early damage, medical treatment, and complications of glaucoma surgery are well worth reading. The chapter on low-tension glaucoma is good and is set out in a fashion to provide practical guidance for the ophthalmic house surgeon. There is a fascinating but perhaps historical chapter on cyclodialysis clefts which includes a description of various ingenious methods of closing the cleft if there is unacceptable hypotony. Chapter 12 is an excellent, compact, and up-to-date summary of laser surgery which covers the successes and limitations of the technique. It is stated, however, that there is a good response to laser trabeculoplasty in aphakic eyes, which conflicts with the opinion of nearly all other authors.

There is a degree of imbalance in the subject matter. On trabeculectomy there is very little indeed. Does this reflect an American aversion to drainage surgery or is the operation now so routine worldwide that extensive discussion is unnecessary? The need for preliminary paracentesis is emphasised, but most surgeons who perform trabeculectomy never do it, and it seems a superfluous step. The final chapter on drainage implants provides a unique background description which will be valuable for those surgeons now taking up this promising technique even if their chosen tube implant is not that used by the authors. JEFFREY L JAY

Cutaneous Abnormalities of the Eyelid and Face: An Atlas with Histopathology. By DON G GRIFFITH, STUART J SALASCHE, DONALD E CLEMONS. Pp. 367. £135·00. McGraw-Hill: Maidenhead, Berks. 1987.

This atlas illustrates just over 200 skin conditions which might confront and confuse the non-dermatologist. In mind are ophthalmologists, plastic surgeons, and optometrists. The authors—two dermatologists and an ophthalmologist with other contributors—aim at a ready reference with abundant illustrations, offering easy access to the conditions included. The care taken in the design and layout of the book has helped to achieve these aims.

After a (perhaps too brief) review of eyelid anatomy and histology the conditions described are grouped by pathology into 11 main parts with subsections. For example, Part 1 entitled, 'Multisystem processes involving the eyelid', is subdivided into dermatoses and hypersensitivity, vesicobullous diseases, systemic and metabolic diseases, connective tissue diseases, and phakomatoses. Fifty separate diseases are described in this part. The other 10 parts range from pigmentary problems to parasitic processes, focal insults to fungal diseases. Two hundred and four conditions in all are described. The text is concise and appears on the left hand pages. The brief discussions include pathogenesis, clinical features (not confined to the skin condition), natural history, and treatment. Key features are highlighted and the histopathology is inset. On the right hand pages, always within sight of the relevant text, are the clinical illustrations, mostly of excellent quality, and the histopathology, which is in black-and-white. A supporting bibliography of references (to 1985) completes the coverage of each condition, and a useful glossary of dermatological terms is thoughtfully placed at the end of the atlas.

The text is carefully compiled and easy to read. The histopathology illustrations are of good quality, but the use of colour and the addition of marks to highlight important features would have enhanced their value to the non-pathologist. This atlas is a pleasure to read and will appeal to ophthalmologists. Its price, unfortunately, may relegate it to the library. A G TYERS

Clinical Ophthalmic Pharmacology. Eds. DAVID W LAMBERTS and DAVID E POTTER. Pp. 588. £47·50. Churchill Livingstone: Edinburgh. 1987.

This is a multiauthor textbook of ophthalmic pharmacology which presents the subject in a remarkably comprehensive and up-to-date fashion. It is liberally annotated with references to original literature, which would make it an excellent jumping-off point for a specialist study in the field. In this it has no competitor, and I shall keep it for reference purposes.

Most of the chapters, divided largely into drug groups, are well constructed and easy to read, though they lack the wealth of illustration which is to be found in Havener's *Ocular Pharmacology* and which so helps to show the subject as something dynamic. But there are innumerable tables of useful information, including a remarkable 30-page appendix of data on ocular penetration of antibiotics (albeit much of it derived from studies on rabbits), as well as text which explores mechanisms of drug action in an exciting way.

It is not a book for the practising ophthalmologist or for a diploma candidate, who will need something with rather less detail, and the busy reader may be annoyed by some of the repetition. Systemic effects of timolol eyedrops, for example, are discussed three times by different authors (in chapters on antiglaucoma therapy, drugs and the autonomic nervous system, and systemic effects of topical applications), but none mentions their possible implications for the control of retinal blood flow. Some tighter editorial control might have made the whole more coherent. But it is a useful source of information and it is good value for money. Libraries serving the needs of postgraduates should buy it. S E SMITH

Ophthalmic Plastic and Reconstructive Surgery. Vols 1 and 2. By BYRON C SMITH. 1449. £189·00. Blackwell: Oxford. 1987.

This is a two-volume text comprising 17 sections and 81 chapters. The authors number more than 100. Most are American: all are specialists within their own fields, many of international standing.

The text is clearly indexed and extremely comprehensive with many excellent illustrations and over 3000 references. Many of the chapters are outstanding, but the sections on radiology, blepharoptosis, eyelid tumours, craniofacial abnormalities, and socket surgery are worthy of special mention.

As is invariably the case with any multiauthored book a certain amount of duplication exists. Some of the procedures discussed reflect the predominantly American authorship and are at variance with the accepted teaching on this side of the Atlantic The only major criticism is that of certain important omissions in the section on eyelid malpositions. Lid surgery in the management of trichiasis merits a mere five lines, while no specific mention is made of upper lid entropion, an astonishing exclusion since seven million people in the world are blind from trachoma. Similarly the surgical management of cicatricial and congenital lower lid entropion is not covered.

In conclusion, the authors' objective of a 'unified and complete reference work on ophthalmic plastic surgery' is largely achieved. The editors are to be congratulated. Virtually all aspects of this rapidly expanding field are covered in an up-to-date, extensively referenced, well written, and beautifully illustrated text. These volumes should be regarded by all those interested in this specialty as the current, definitive reference textbook.

R N DOWNES

Note

European Ophthalmic Pathology Society

The 27th Annual Meeting of the European Ophthalmic Pathology Society was held in Utrecht, the Netherlands, on 7–10 June 1988, at the invitation of the Organising Secretary, Dr A Hamburg. Professor F A Jakobiec, of New York and the Verhoeff Society, was the honoured guest. Twenty-nine ordinary members of the society also attended the meeting together with Professor N Ashton, honorary life president, and Professor W A Manschot, emeritus member.

The following papers were presented at the scientific meeting: Anaplastic carcinoma of the lacrimal gland presenting with recurrent subconjunctival haemorrhages and displaying incipient sebaceous differentiation (F A Jakobiec, USA) Granulomatous reaction in a malignant melanoma of the choroid (K Arnesen, Norway). Lymphoma in an extraocular muscle (E Balestrazzi, Italy) Local ischaemia of the optic nerve (M Brihaye, Belgium). A clinically unpigmented melanoma of the limbus (A Brini, France). Merkel-cell tumour of the eyelid?–A case for diagnosis (J Cunha-Vaz, Portugal). Refsum's disease (heredopathia atactica polyneuritiformis) (B Daicker, Switzerland). Optic nerve glioma with an intraocular tumour in neurofibromatosis (D de Wolff-Rouendaal, Netherlands). Presumed tumour of the optic disc (P C Donders, Netherlands). Monoclonal corneal gammopathy (A Garner, UK). Orbital involvement in a non-Hodgkin lymphoma of high malignancy mimicking a myeloma (G J Goder, GDR). A peculiar epibulbar growth of a conjunctival melanoma (R Haddad, Austria). Anteriorly luxated lens (A Hamburg, Netherlands). Siderosis bulbi and glaucoma (M Hanssens, Belgium), Epiretinal melanosis in a Greenlander (O A Jensen, Denmark). Metastatic tumour in the orbit from the liver (E Kock, Sweden), Aesthesioneuroepithelioma invading the orbit (E Landolt, Switzerland). Unusual orbital lesion—case for diagnosis (Z Latkovic, Yugoslavia). Medulloepithelioma of the ciliary body (W R Lee, UK). Ocular histopathology in a child and a fetus affected with sialidosis (J Libert, Belgium). Choroidal metastasis of an oesophageal squamous cell carcinoma (C M Mooy, Netherlands). AIDS ocular pathology with toxoplasmosis and CMV retinitis (J Mullaney, Ireland). Band keratopathy (P Naeser, Sweden), Marfan's syndrome (G O H Naumann, FRG). Walker-Warburg's syndrome (J U Prause, Denmark). Limbal carcinoma with basaloid differentiation (M Quintana, Spain). Syphilitic chorioretinitis (P A Smith, UK). I O crystals in diffuse myelomatosis with amyloidosis (F H Stefani, FRG). Malignant schwannoma of the orbit in von Recklinghausen neurofibromatosis (M Sterkers, France). Rare intra- and extrabulbar tumour (I Strempel, FRG). Epikeratophakia (A Tarkkanen, Finland). A case of endogenous fungal endophthalmitis (M Uyama, Japan). Pseudolymphoma of the conjunctiva (J Van Baarlen, Netherlands). Angioleiomyoma of the ciliary body (H E Volcker, FRG). Angiomatosis retinae in familial von Hippel-Lindau disease (F Weber, Switzerland) Pleomorphic adenoma of the lacrimal gland (H Witschel, FRG). Chronic human ocular chalcosis (Z Zagorski, Poland).

The next meeting will be held in Copenhagen, Denmark, May 1989, and Professor O A Jensen will act as Organising Secretary.

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Contents

Prevalence and causes of blindness in the Northern Transvaal PIUS J M BUCHER AND CAREL B IJSSELMUIDEN *page* 721

Sickle cell retinopathy in Jamaican children: further observations from a cohort study J F TALBOT, A C BIRD, G H MAUDE, R W ACHESON, B J MORIARTY, AND G R SERJEANT *page* 727

How do general practitioners manage eye disease in the community? P J McDONNELL *page* 733

Visual recovery in orbital vasculitis A BAGEGNI, R W LYNESS, P B JOHNSTON, AND J F DOUGLAS *page* 737

Effect of intraocular lens implantation on combined extracapsular cataract extraction with trabeculectomy: a comparative study R NEUMANN, M ZALISH, AND M OLIVER *page* 741

The consensual ophthalmotonic reaction MARY V GIBBENS *page* 746

Sympathetic influences on the consensual ophthalmotonic reaction MARY V GIBBENS *page* 750

Retinal circulation during a spontaneous rise of intraocular pressure JUAN E GRUNWALD, CHARLES E RIVA, AND DAVID M KOZART *page* 754

Stereoscopic evoked responses to crossed and uncrossed disparity accompanying simulated refractive error R A NEILL, P DUNLOP, D B DUNLOP, B FENELON, AND C DUNLOP *page* 759

Medulloepithelioma (diktyoma) C R CANNING, A C E McCARTNEY, AND J HUNGERFORD *page* 764

Analysis of the factors involved in cosmetic failure following excision of the eye D L SMERDON AND G A SUTTON *page* 768

Marginal corneal abscess associated with adult chlamydial ophthalmia S DAROUGAR AND N D VISWALINGHAM *page* 774

Optic nerve involvement in a case of methanol poisoning peter naeser *page* 778

Haemangiopericytoma of the lacrimal sac: a case report L CARNEVALI, F TRIMARCHI, R ROSSO, AND M STRINGA *page* 782

Primary Ewing's sarcoma of the orbit presenting with visual loss G WOODRUFF, P THORNER, AND B SKARF *page* 786

Ocular involvement in sinus histiocytosis with massive lymphadenopathy ZEYNEL A KARCIOGLU, BELU ALLAM, AND MICHAEL S INSLER *page* 793

The 'poor man's' Landers lens LARRY BENJAMIN *page* 796

Book reviews *page* 799

Note *page* 800

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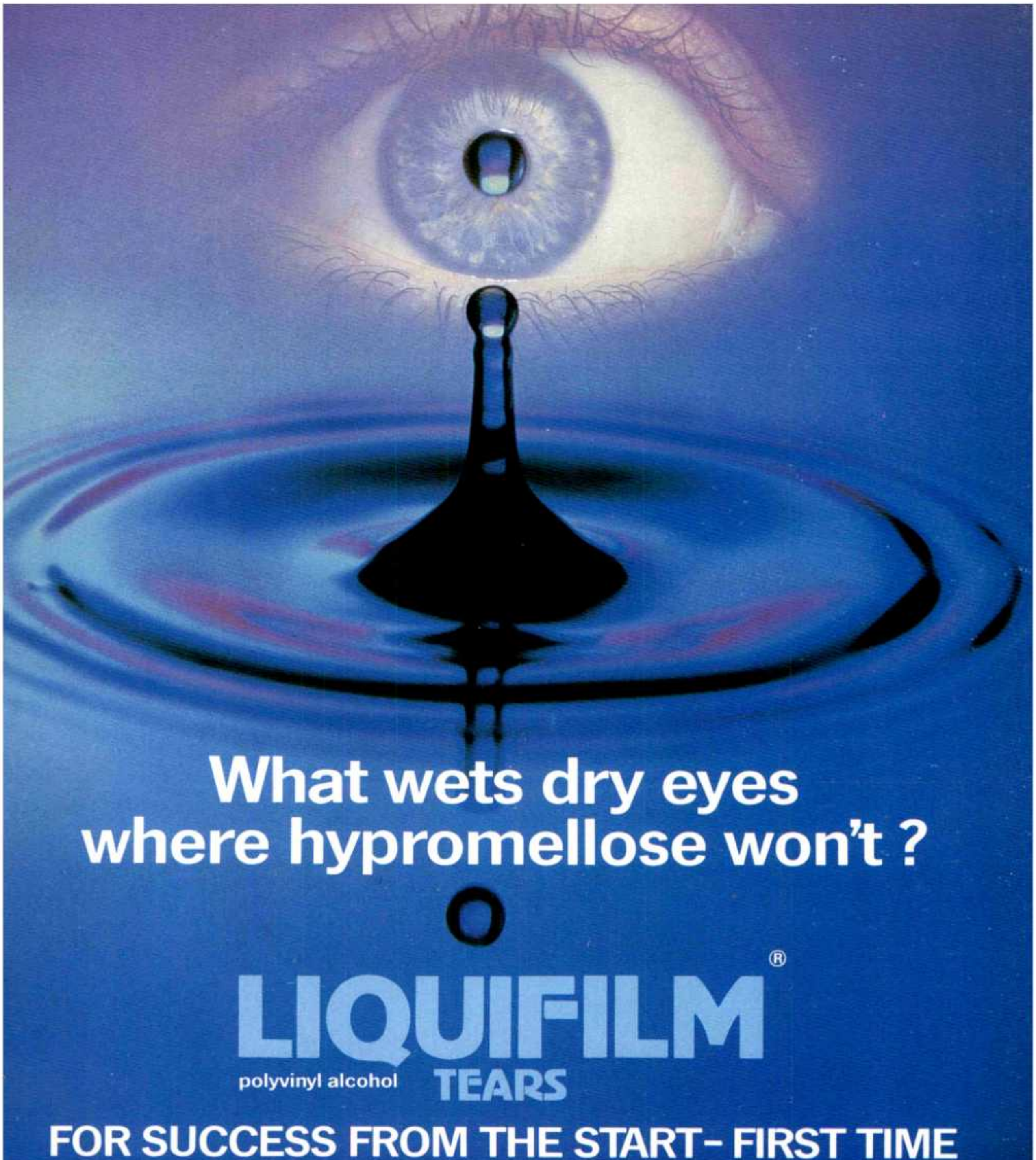
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Reference 1. Kralian LM, American Journal of Optometry and Physiological Optics 1986; **63** (No. 4): 304-308.

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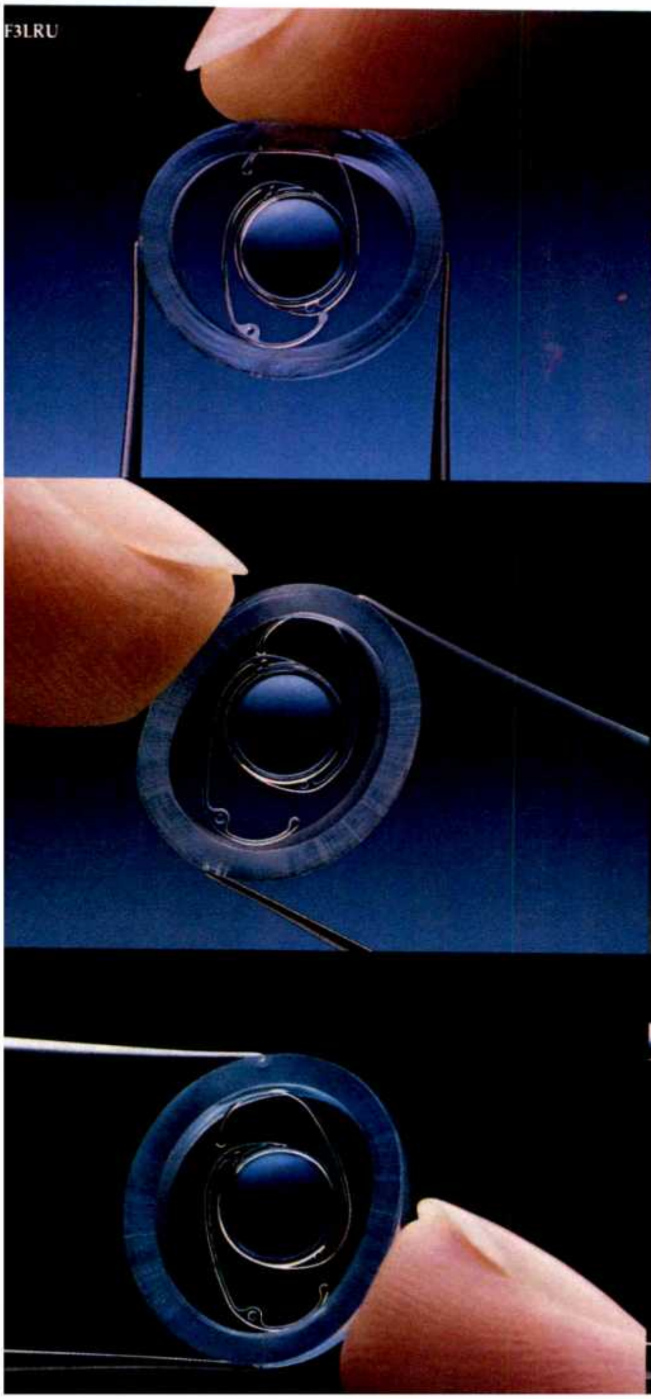

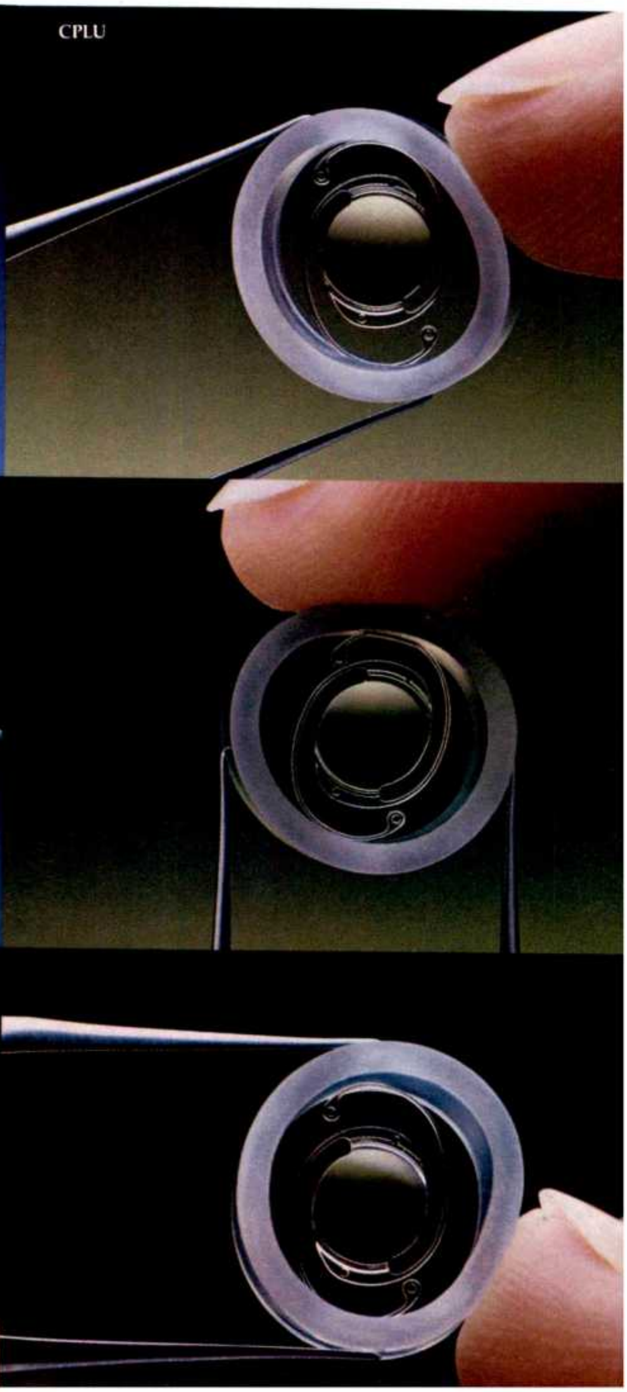

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British Journal of Ophthalmology, 1988, **72**, 801–803

A rapid method of grading cataract in epidemiological studies and eye surveys

V MEHRA[1] AND D C MINASSIAN[2]

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SUMMARY A rapid method of grading clinically important central lens opacities has been developed for use in eye surveys and in epidemiological studies of cataract and has been field-tested in a specifically designed observer agreement study in a survey of a rural community in Central India. The grading method is based on simple measurement of the area of lens opacity that obscures the red reflex relative to the area of clear red reflex, as visualised through the undilated normal pupil. Good to almost perfect agreements were attained between two ophthalmologists and two trained ophthalmic assistants for overall grades of central lens opacity. Most disagreements were trivial in nature and were concerned with difficulties in distinguishing grade 0 from grade 1, and with hazy appearance of the red reflex in high myopes and in cases of early nuclear sclerosis. Teaching materials including video tape and slides for training survey teams and other workers are in preparation

Prevalence surveys of blindness and eye disease require a reliable, repeatable, and rapid method for grading clinically important cataract, as do certain population based epidemiological studies of cataract, such as our programme of collaborative research into the incidence and causation of blinding cataract in Central India. A rapid method for grading central lens opacities has been developed and used in our collaborative studies.[1] The method focuses on grading lens opacities that are central, visible through the undilated pupil, and likely to interfere with vision. This paper reports on a study designed specifically for field assessment of the grading technique in a rural community in Central India.

Material and methods

A village community in the Arang block of Raipur District in Central India was surveyed by a team of four examiners and supporting auxiliaries. Immediately prior to the study the four examiners attended intensive sessions of training and standardisation exercises for a period of one week at the base hospital. Two ophthalmologists (VM and DCM) and two ophthalmic trained assistants (MT and SS) carried out the eye examinations and graded the lens opacities. Visual acuities were measured by two auxiliaries who did not take part in the grading. Every eye was examined by all four examiners located at four separate stations in a darkened room in the village. Each examiner recorded his findings on separate record sheets which were later collated at the end of the field work. There were no consultations or further standardisation exercises during the field work.

GRADING OF CATARACT

The eye examinations were carried out with direct ophthalmoscopes fitted with new batteries at the beginning of the session. The red reflex was visualised through the undilated pupil with a direct ophthalmoscope set at +2 D and held at approximately ⅓ m from the eye. Opacities that partially obscured the red reflex were scrutinised from several angles of view to determine their location in relation to the lens. But the final assessment of the area of lenticular opacity was made by directing the light source away from the macula, towards the nasal portion of the retina, at an angle of approximately 25° to the visual axis, in order to avoid excessive constriction of the pupil beyond the usual size in daylight. Opacities in the lens that disturbed the red reflex were distinguished from non-lenticular opacities

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Table 1 *Rules for grading central lens opacities*

Grade of central lens opacity	*Criteria*
0	Clear red reflex, no opacities
1	Few small dot opacities in the lens appearing as tiny scattered dark spots in the red reflex. Maximum area occupied by the dots $1\ mm^2$
2A	Lens opacity obscuring part of red reflex. Area obscured is smaller than area of clear red reflex
2B	As 2A but area obscured equal to or larger than area of clear red reflex
3	Lens opacity totally obscuring the red reflex
4	Aphakia or displaced lens
5	Unable to assess red reflex owing to corneal opacity etc.

Table 2 *Agreement between pairs of four examiners in grading central lens opacities. The table shows weighted and unweighted kappa values as measures of agreement*

Examiners	*Kappa values across all grades*	
	Weighted	*Unweighted (SE=0·03)*
VM and DCM	0·962	0·885
VM and MT	0·932	0·813
VM and SS	0·934	0·848
DM and MT	0·945	0·845
DM and SS	0·929	0·834
MT and SS	0·918	0·820

VM and DCM are ophthalmologists, MT and SS are ophthalmic assistants.

and were graded according to the criteria set out in Table 1.

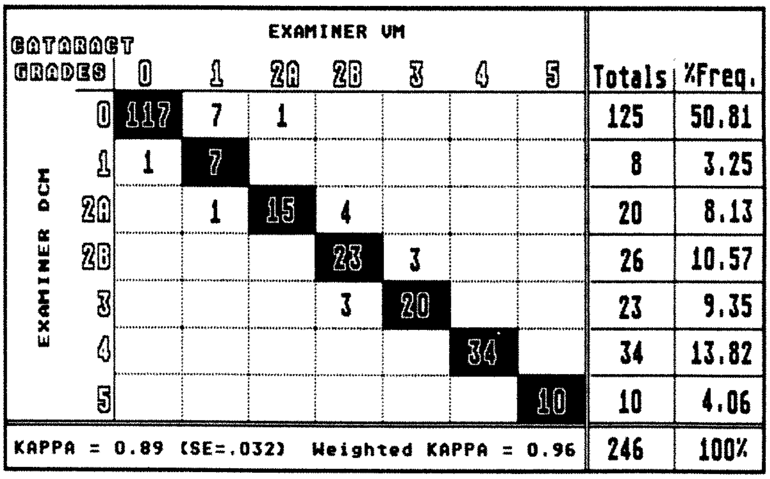
ANALYSIS OF DATA

The record sheets were collated and the data were entered into a portable microcomputer (Epson PX-8) at the end of the day. The data entry, tabulation, and statistical analysis software were developed at the ICEH specifically for this purpose.

The degrees of agreement between the examiners were measured by computing kappa statistics. These evaluate the amount of observed agreement beyond chance, relative to the maximum possible agreement over and above chance.[2] Thus in most situations a kappa value of 0·81–1·0 indicates almost perfect agreement, and kappa values of 0·61–0·80 suggest substantial agreement.[3] Weighted kappa values were also computed by means of weights as suggested by Cicchetti and Allison.[4]

Results

Each of the four examiners assessed and graded 246 eyes (123 persons), making a total of 984 examinations. The age distribution of the sample was somewhat skewed towards the older age groups, the youngest age being six years. The frequency of occurrence of the various grades of central lens opacities according to one of the ophthalmologists is shown in the marginal totals of Fig. 1. As expected, the eyes with cataract are over represented in the sample. The 'agreement cells' in Fig. 1 show the number of eyes that received identical grades from the two ophthalmologists. Disagreements were few and trivial in nature as shown in the body of Fig. 1. The kappa statistic and its standard error indicate almost perfect overall agreement between the two ophthalmologists. The grade-specific agreements between the two ophthalmologists were also excel-



CATARACT GRADES	EXAMINER VM 0	1	2A	2B	3	4	5	Totals	%Freq.
EXAMINER DCM 0	117	7	1					125	50.81
1	1	7						8	3.25
2A		1	15	4				20	8.13
2B				23	3			26	10.57
3				3	20			23	9.35
4						34		34	13.82
5							10	10	4.06
KAPPA = 0.89 (SE=.032) Weighted KAPPA = 0.96								246	100%

Fig. 1 *Agreement between two examiners (ophthalmologists VM and DCM) in grading central lens opacities: the shaded agreement cells show number of eyes that were given identical grades by the two examiners.*

lent for all grades (except for grade 1), with kappa values ranging from 0·8 to 1·0. The kappa for grade 1 was lower at 0·6. However, the disagreements were clinically of little importance and arose largely from difficulties in distinguishing grade 0 from grade 1.

The agreement between each ophthalmologist and each of the ophthalmic trained assistants was remarkably similar to that found between the two ophthalmologists. The relevant kappa values are reported in Table 2. The total time taken by the slowest examiner to grade 123 persons (246 eyes) and record the findings was about three hours, averaging at 1·5 minutes for grading one person.

Discussion

The survey study was designed specifically for assessment of the new grading method. The sample comprised a good mixture of various categories of central lens opacity and provided adequate numbers of eyes in each grade to enable assessment of grade-specific and overall degrees of agreement. The over-representation of cataract cases and aphakics was expected and hoped for, as no attempt had been made to examine every resident of the village or to take a random sample of a defined population.

The agreements attained were well above that generally considered satisfactory in prevalence surveys of eye disease and also in epidemiological studies where higher kappa values of more than 0·75 or so are demanded. The disagreement could be attributed to two main problems: distinction between grade 0 and grade 1, and 'hazy' appearance of the red reflex in high myopes and cases of early nuclear sclerosis.

Table 3 *Correlation of visual acuity with grades of central lens opacity Aphakic eyes and those that could not be assessed for cataract (grade 5) are excluded*

Visual acuity	*WHO* category of visual impairment*	*Grades of cataract as graded by ophthalmologist (DCM)*					
		0	*1*	*2A*	*2B*	*3*	*Totals*
6/6–6/9	0	97 100%	0 0%	0 0%	0 0%	0 0%	97
6/12–6/18	0	23 61%	7 18%	8 21%	0 0%	0 0%	38
6/24–6/60	1	5† 16%	1 3%	10 31%	16 50%	0 0%	32
5/60–3/60	2	0 0%	0 0%	2 20%	7 70%	1 10%	10
2/60–1/60	3	0 0%	0 0%	0 0%	3 23%	10 77%	13
<1/60	4,5	0 0%	0 0%	0 0%	0 0%	12 100%	12
Totals		125	8	20	26	23	202

*The WHO categories of visual impairment are described in an offset publication No.54 available from the WHO, Geneva.
†Four of these were high myopes

As expected, there was good correlation between the cataract grades and levels of visual impairment. The details are shown in Table 3.

Finer grading of central and other lens opacities is necessary for follow-up studies or clinical trials that aim to quantify small changes in the area or density of opacification. However, clinical grading techniques are by and large inadequate for such studies, which require more objective methods of standardised documentation and quantitative image analysis techniques.[5-8]

Teaching materials including video tape, photographic slides, and prints of the various grades of central lens opacity for training survey teams and other workers are in preparation.

Our thanks to Mr Mohan Tiwari and Mr Shankar Sahu as two members of the examination team, Mr Santosh Agrawal for helping to organise the field work and providing a large darkened room in the village, other staff of Chattisgarh Eye Hospital as supporting members of the survey team.

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A case-control study of cataract in Oxfordshire: some risk factors

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SUMMARY Three hundred patients with cataract and 609 control subjects with the same age-sex distribution were interviewed in a study of cataract in Oxfordshire, England. The risks associated with severe diarrhoea, glaucoma, and work on a military base have been demonstrated. Population attributable risks were calculated for those and other risk factors.

Cataract is the major cause of blindness worldwide and yet it is frequently stated that most cataracts are of unknown aetiology. In the Western world it usually occurs late in life and has therefore been called senile cataract. In some third world countries it is more prevalent than in the West and develops at an earlier age. Our suggestion that diarrhoea might be an important factor in these countries[1] has been supported by the results of a careful study from India.[2] Several risk factors for cataract, including diabetes, glaucoma, and high levels of plasma glucose and urea, were identified in a study in Edinburgh,[3] but they did not include diarrhoea. We have conducted a similar study in Oxfordshire with particular interest in diarrhoea, medical and drug history, smoking, drinking, and place of work. It was necessary to obtain information on past events and practices, because cataract may take many years to develop following exposure to a risk factor. Some results of this survey have been published in two short papers.[4,5]

Our aim was to identify major risk factors for cataract of any type. Our definition of cataract was such cases as required surgery.

Subjects and methods

Cases were those patients aged between 50 and 79 years admitted to the Oxford Eye Hospital for cataract extraction. Three hundred cases were interviewed on the ward. None refused.

The Oxford Eye Hospital is a National Health Service (NHS) hospital serving the people of Oxfordshire and parts of Berkshire and Buckinghamshire. It is the only NHS eye hospital in this area. The hospital notes were not looked at before the interview, so it would not be possible to select particular groups (for example, those with arthritis) for interview. There were no other selection criteria apart from age (50–79).

CONTROLS

Four groups of controls were recruited. The first group consisted of inpatients at the Ear, Nose, and Throat Department and patients in the Dermatology Department (Slade Hospital). They were interviewed in hospital after being asked if they had cataract. Any giving a positive response were excluded. Subjects aged 50–79 years were recruited, but towards the end of the study recruitment concentrated on older subjects so that the age-sex distribution matched the cases. These departments are also NHS hospitals coming under the same area authority and serving essentially the same population (563 000) as the Oxford Eye Hospital. As about 95% of the British population is served by the NHS, patients in these hospitals are representative of the population at large within the same region. The ENT department is one minute's walk from the Oxford Eye Hospital. Most of these hospital patients had been admitted for minor surgery and in that sense also were comparable to cases. The dermatology department is also in Oxford.

The other three control groups were identified from the age-sex registers of local general practitioners. This made it possible to match the age-sex distribution to that of cases (Table 1). These com-

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Table 1 *Age-sex distribution of the cases and the different control groups*

Group	*Age group*					
(a) *Percentage of females of each group in each age group (total number=507)*						
	50–54	55–59	60–64	65–69	70–74	75–79
1	6·2	8·6	18·5	19·1	24·1	23·5
2	6·1	10·6	18·2	22·7	22·7	19·7
5	6·1	8·1	21·2	17·2	23·2	24·2
6	6·7	7·9	20·2	16·9	23·6	24·7
7	6·6	7·7	17·6	17·6	28·6	22·0
(b) *Percentage of males of each group in each age group (total number=402)*						
	50–54	55–59	60–64	65–69	70–74	75–79
1	5·8	13·8	18·1	18·8	23·2	20·3
2	5·9	15·7	17·7	17·7	23·5	19·6
5	6·1	10·6	16·7	18·2	25·8	22·7
6	5·3	12·0	17·3	22·7	22·7	20·0
7	4·2	16·7	19·4	15·3	23·6	20·8

Group 1 is the cataract group Groups 2, 5, 6, 7 are the four control groups.

There were 300, 117, 165, 164, and 163 subjects respectively in each group. The mean ages were between 67·1 and 67·8 years for each of the five groups

munity controls were interviewed at home a few days after a warning letter. The three general practice areas were chosen to give a good socioeconomic spread. Two were urban and one covered a nearby large village. Interviews of cases and controls overlapped. Under the NHS 95% of the British population are registered with general practitioners, who form the first source of health care, and hence their age-sex registers are a useful way of identifying controls.

Our control groups included some people with minor opacities of the lens, as we excluded only those who had been told that they had cataract. Such opacities were relatively trivial compared with the cataracts in the cases. (In the chosen age range most people have such opacities[4] and to exclude them would be to restrict the controls to a small subgroup of the population.)

A total of 609 controls were interviewed. Of potential controls about 4% had cataract, while 5% refused or were too ill to interview or spoke no English.

QUESTIONNAIRE

The cases and controls were interviewed in exactly the same way except that potential controls were asked if they had cataract. Informed consent was obtained. Each subject was given a code number, the first digit identifying the control group or case. No other identifier was entered into the computer. Age, sex, weight, and height were recorded. All subjects were asked where they had worked and what occupations they had followed. There were questions on general medical history and ocular history. All were asked if they were short-sighted as a child and further prompted by being asked if they wore spectacles as a child and then what the spectacles were for. Only when the interviewer (RvH) was sure were they counted as myopic when young.[4] They were asked if they had ever had severe diarrhoea lasting four days or more. If they had, the time since the last attack, and how attacks were treated, was recorded. They were asked what drugs they had taken regularly for more than four months at any time in the past. Finally, they were asked their current and past smoking and drinking habits.

DATA ANALYSIS

Data were entered into the University's VAX computer and analysed by the χ^2 test for categorical variables and Student's t test for continuous variables, mostly by means of the SAS statistical package. The data entered into the computer consisted of 66 digits, less than a single line, for each of the 909 subjects. Odds ratios (cross product ratios) were computed from contingency tables and are reported as valid estimates of relative risk. Thus a reported relative risk of 2 for a particular risk factor implies that the exposed group are twice as likely to end up having cataract extraction than those who have had no exposure (or least exposure) to that risk factor.

Confidence intervals were calculated as described in the SAS User's Guide: Statistics version 5. Each factor investigated was first tested on all 300 cases and 609 controls, but interesting results were subsequently studied in subclasses by sex, age group, etc.

Results

After the data file had been checked for obvious errors the comparability of the control groups was examined There were no significant differences between the four control groups in the proportion of subjects reporting no serious illness; hypertension; diabetes; serious illness other than diabetes, renal failure, and hypertension; aspirin consumption; or unknown drugs. Therefore all controls were pooled for most analyses.

At the start of the study we knew there was a possibility of recall bias, especially between hospital and community groups, but the comparisons between the different control groups indicate that little if any recall bias has occurred. Vague categories such as 'other illness' and 'other drug' showed no difference between cases and controls.

Some results of this case-control survey have been published, including the exploration of two risk

Table 2 *Severe diarrhoea as a risk factor for cataract in septuagenarians: contingency table*

	Controls	*Cases*	*Total*
Severe diarrhoea	14	14	28
Without severe diarrhoea	268	123	391
Total	282	137	419
Percentage positive	5·0	10·2	

χ^2 test p=0·043; relative risk=2·18, 95% confidence limits 1 01 to 4·7

factors, diabetes and myopia, showing females to be particularly susceptible[4] and the identification of aspirin-like analgesics as protective factors against cataract.[5]

SEVERE DIARRHOEA

Severe diarrhoea appeared as a marginal risk factor for cataract when comparing all cases and all controls (p=0·05 χ^2 test; relative risk 1·6) but was found to be a stronger risk factor in those aged 70 to 79 years (Table 2). The increased risk in this older group probably relates to severe diarrhoea during military service in the Far East between 1939 and 1945. Nevertheless, severe diarrhoea is only a marginal risk factor in the Oxford population.

RENAL FAILURE

Renal failure appeared as a powerful risk factor with a relative risk of 12·4 (2·4 to 65). With only one control out of 609 reporting renal failure compared with six out of 300 cases, the χ^2 test was not applicable, but Fisher's exact test (2-tail) gave a probability of 0·006. Hence, renal failure was the most powerful risk we encountered in the total population, though affecting a small proportion of cases (2%). Four of the seven renal failure patients were also insulin-taking diabetics, all of them cataract cases. None of them reported taking steroids. One case and one control reported severe diarrhoea.

GLAUCOMA

Glaucoma appeared as a powerful risk factor (p<<0·001 and relative risk 5·9) as shown in Table 3. The relative risks were high for each sex taken separately (5·4 for men, 6·7 for women), and high for both younger (3·6) and older (8·5) subjects. The cholinesterase inhibitors which were widely used to treat glaucoma are known to cause cataract[7] but lenses of glaucoma patients opacify even without this therapy,[8] and it appears that the cataract risk associated with glaucoma is caused by a combination of the disease itself and the treatment applied.[9]

It could be suggested that as the cataract cases are seen regularly in the Eye Hospital that their glaucoma is more likely to be known than that of the control patients. In theory this would tend to make any ocular condition appear as a risk factor. However, analysis of the data for all ocular problems apart from cataract, glaucoma, and myopia did not show this pooled category to be a risk factor. We consider therefore that the effect of a difference in ophthalmic care was negligible. Alternatively it could be suggested that cataract patients with glaucoma are more likely to have cataract extractions than those without glaucoma but similar arguments apply. It is most unlikely that the 6-fold increase in risk associated with glaucoma could be explained in this way.

PLACE OF WORK

All subjects were asked where they had worked, and a note was made of the three where they had worked for longest—in order. Certain major employers in the Oxford area were scored individually, for example, the University, the car industry, military bases, and publishing. Only one of these appeared as a significant risk factor and then only when it was the main place of work. Those whose major work place had been on a military base were more than twice as likely to have cataract (Table 4). Only one of these was female. For males only, the relative risk was 2·37 (1·07 to 5·3) with p=0·03.

The explanation for the association between cataract and work on a military base is not obvious. There is the possibility of encountering microwave (radar) and other equipment, but there is also the possibility that this group tended to drink and smoke more than others.

Table 3 *Glaucoma as a risk factor for cataract*

	Controls	*Cases*	*Total*
With glaucoma	8	22	30
Without glaucoma	601	278	879
Total	609	300	909
Percentage positive	1·3	7·3	

χ^2 test p<0·001; relative risk=5 95; 95% confidence limits 2 6 to 13·5.

Table 4 *Work on military bases and cataract*

	Controls	*Cases*	*Total*
Military base	13	14	27
Elsewhere	596	286	882
Total	609	300	909
Percentage positive	2·1	4·7	

χ^2 test p=0 034, relative risk=2 24; 95% confidence limits 1·04 to 4·84

'Heavy beer drinking' and 'heavy smoking' were found to be risk factors for cataract in this study[10] and could be responsible for the apparent danger of military bases. With only 14 military cases and 13 military controls (Table 4) stratification of beer drinkers and of cigarette smokers into four dose groups gave numbers too small for reliable analysis. Omitting only the 'heavy beer drinkers' (more than 2 pints (950 ml) per day) from the analysis leaves work on a military base as a risk factor ($p=0{\cdot}021$, relative risk=2·5), so beer drinking cannot explain this risk. However, after omission of 'heavy smokers' (defined in Harding and van Heyningen[10]) from the analysis the risk associated with military bases is no longer significant ($p=0{\cdot}089$), though workers on military bases were still overrepresented among cases (apparent relative risk 1·97). Analysis for interactions by means of GLIM (Royal Statistical Society, Edinburgh) indicated that the risk associated with military bases was not the result of either heavy smoking or drinking.

COMBINATION OF RISK FACTORS

It is difficult to study interacting factors in any detail because the numbers reporting any two specific conditions are small. The two most powerful risk factors were glaucoma (Table 3) and diabetes.[4] The four subjects in the study with both glaucoma and diabetes were all cases. Myopia early in life was also a risk factor.[4] Myopia early in life was investigated because a myopic shift occurs at an early stage in the development of nuclear cataract. The four subjects reporting both myopia and diabetes were all cases. Of three subjects reporting myopia and glaucoma two were cases. Four of the five subjects reporting both severe diarrhoea and diabetes were cases. Three of the four subjects reporting both severe diarrhoea and glaucoma were cases. Although the data are limited, there is an impression that pairs of factors may be additive.

ATTRIBUTABLE RISK

It is of interest to note not only how powerful a risk factor may be but also, on the assumption of a causal relationship, how much cataract is attributable to each factor. We therefore calculated the population attributable risk percentage (PARP) for cataract by the method of Cole and MacMahon.[11] The estimation of attributable risks from case-control studies depends on the incidence of the disease being low. Although the incidence of lens opacities is high in those aged 50 to 79,[4] the incidence of cataract as we define it is low, less than 1 in 1000 total population of this region, therefore the calculation is valid. Of the risk factors identified in this study, diabetes had the highest attributable risk followed by early myopia and glaucoma (Table 5). The other risk factors accounted for less than 5% of cataract each.

Table 5 *Population attributable risk percentages (PARPS) for cataract*

Factor	*PARP (%)*
Diabetes	11·9
Myopia	6·9
Glaucoma	6·1
Steroids	4·7
Severe diarrhoea	4·3
'Heavy smoking'	2·6
'Heavy drinking'	2·6
Work on military bases	2·5
Spironolactone	2·3
Nifedipine	2·0
Renal failure	1·8

Data for the drugs, smoking, and drinking from Harding and van Heyningen.[10]

PARPS are a measure of the proportions of cataract in Oxfordshire that is associated with each risk factor. They indicate the proportions of cataract that could be prevented by elimination of each risk factor.

Discussion

This survey was concerned with the risk factors for all cataracts. We did not divide cataracts into classes. Subtle classification rapidly diminishes the number available for analysis. Known risk factors such as diabetes do not produce a single morphology of cataract in the age range studied, and there is evidence for common pathways in mechanisms of cataract formation.[4] The inclusion of some controls with minor lens opacities will have made it a little more difficult for us to identify risk factors but would not cause us to make type I errors (false positive results). Severe diarrhoea has been proposed as a major cause of cataract in tropical countries to account for their excess of cataract.[1] Subsequently the role of 'life-threatening diarrhoea' in cataract in Raipur, India, was established by a case-control study.[2] It is perhaps surprising to find severe diarrhoea as a risk factor in the Oxford population, but it is not a powerful factor here. The relative risk was much greater in the study in India, where diarrhoea is both more common and more severe.[2]

The results of this study strengthen the view that cataract can be a complication of renal failure.[4] This is the first study to identify the relative risk of cataract associated with renal failure, and it is notably high. Several factors that could be important in the aetiology of cataract in renal failure patients could also have a role in cataract following severe diarrhoea.[1,4] These include cyanate formed from urea and the osmotic stress. The suggestion that steroid therapy could have a role in cataract in renal failure can be ruled out in this study, because none of the renal failure patients reported taking steroids. Cyanate binds to lens proteins, producing several changes corresponding to those found in human cataract. These include conformational changes to the proteins and cross-linking.[1,12] Cyanate causes opacification of lenses in vitro[13] and in vivo.[14]

Glaucoma appeared as a powerful risk factor in this study, though none of the subjects reported taking cholinesterase inhibitors. The increased susceptibility to cataract is probably due to glaucoma itself or the surgery to alleviate it. The explanation for the association between cataract and work on a military base is not obvious. There is the possibility of encountering microwave (radar) and other equipment, but also this group tended to smoke more than others. It seemed possible that the result might have arisen because military personnel usually do not register with a general practitioner, but in the age range studied we had only ex-military people, and the relationship persisted in septuagenarians who had retired long before.

The data on pairs of risk factors are limited by the size of this study, but they support the idea that apparently distinct factors can act together in the formation of cataract. The only previous attempt to calculate attributable risks for cataract was in the study in India, where almost 40% of the cataract could be attributed to 'life-threatening diarrhoea'.[2] In Oxfordshire no single risk factor accounts for so high a proportion (Table 5). In India, at least in Raipur, improved sanitation might in the long term eliminate up to 40% of the cataract burden; it would have little effect in Oxford. Here a programme for decreasing cataract would have to look at a number of factors, none of them easily removed. Diabetes cannot be avoided, though one would hope that improved control of blood glucose would lessen the risk. Weale[15] suggested that overcorrection of myopes in their late 20s to maintain their lenses in a slightly accommodated state would decrease their excess risk of cataract.

The link between glaucoma and cataract may relate to the severity of the glaucoma or to the trauma of operations to alleviate glaucoma, so it will be difficult to eliminate this risk. Use of steroids will decline only as alternative drugs emerge. One would think that the risk of diarrhoea-related cataract would be diminishing rapidly in England, but our sewage system is falling into disrepair and the incidence of diarrhoeal disease is increasing rapidly in some areas.

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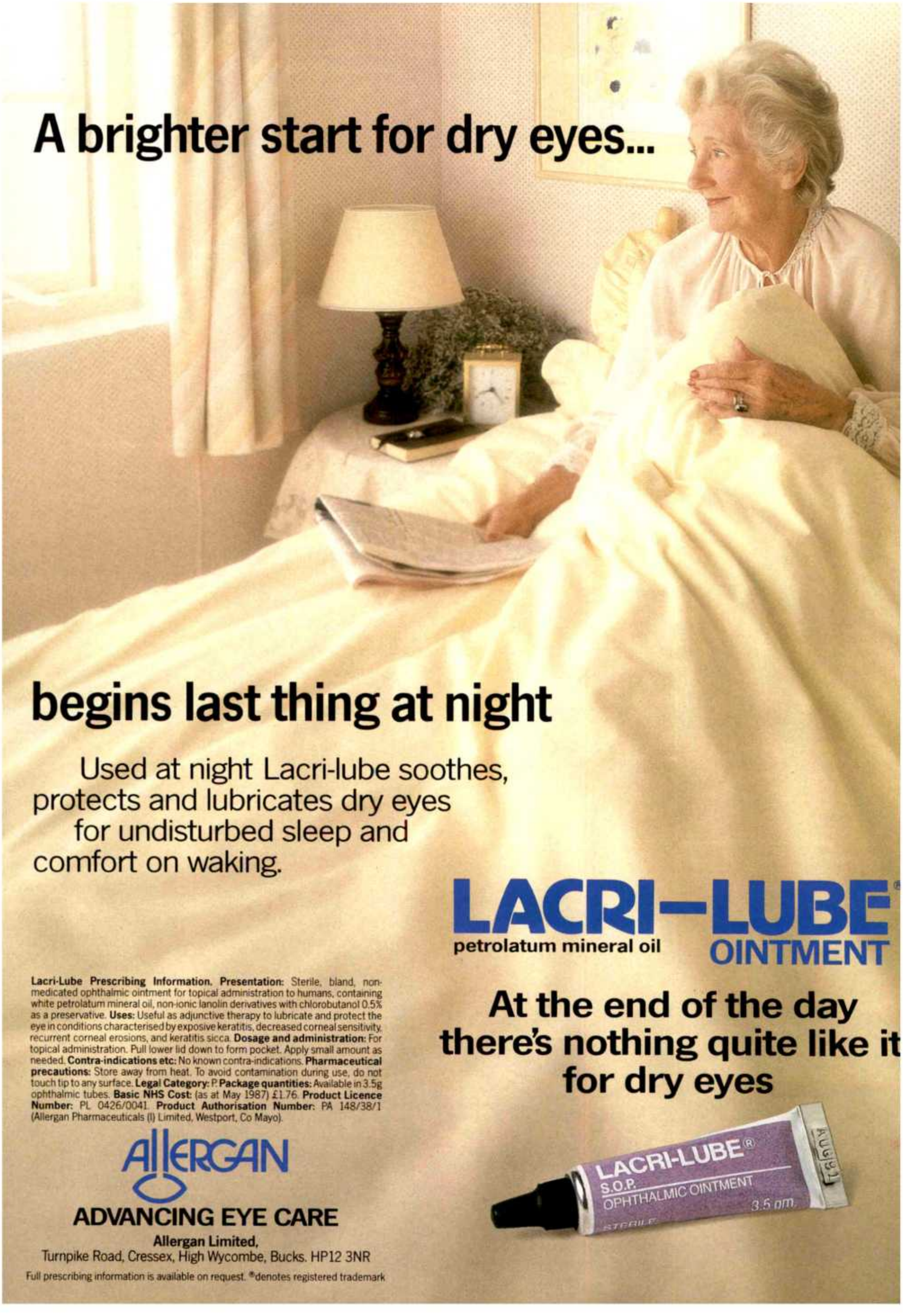

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Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide

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SUMMARY A case-control study of cataract in Oxfordshire explored the risks and benefits associated with a variety of drugs. Steroids including the diuretic spironolactone, nifedipine, heavy smoking, and beer drinking were associated with a raised risk. On the other hand aspirin-like analgesics (paracetamol, ibuprofen, aspirin, etc.) appeared to protect against cataract. Cyclopenthiazide appeared to provide a similar protection.

Cataract is the major cause of blindness worldwide, but only recently have some major risk factors in cataract been elucidated in different countries.[1-3] We conducted a case-control study of cataract in Oxford and have reported on the risks associated with diabetes, myopia, severe diarrhoea, glaucoma, and employment on a military base.[3,5] Here we report on drugs that appear to be risk factors for cataract in Oxford, and on drugs that appear to have protected against cataract

Material and methods

Three hundred cases and 609 controls aged 50–79 were interviewed for this study. Cases were those patients aged between 50 and 79 having cataract extracted in the Oxford Eye Hospital. Cases and controls had the same age-sex distribution.[5] Details of the recruitment, questionnaire, and data analysis have been reported.[5] The subjects were asked what drugs they had taken regularly for at least four months at any time in the past. They were also asked about their current and past smoking and drinking habits. In the analysis of the data odds ratios were computed from contingency tables and are reported as valid estimates of relative risk. Thus a reported relative risk of 2 for a particular factor implies that the group exposed to that factor are twice as likely to be admitted for cataract extraction as those not exposed to that factor. Conversely a relative risk of 0·5 implies that the group exposed to the factor are protected against cataract, being only half as likely to have a cataract extracted as the unexposed group.

Results

STEROIDS

Long-term steroid therapy causes posterior subcapsular cataract,[4] but in the present study consumption for as little as four months was scored. Nevertheless steroids emerged as a significant risk (Table 1). The steroids most commonly reported were prednisolone and spironolactone with a risk

Table 1 *Steroids as a risk factor for cataract*

	Controls	*Cases*	*Total*
Steroid	38	32	70
No steroid	571	268	839
Total	609	300	909
Percentage positive	6·2	10·7	

χ^2 test, $p<0·025$; relative risk=1·79; 95% confidence limits=1·09 to 2·93

Table 2 *Diuretics and cataract*

	Controls	*Cases*	*Total*
Reporting diuretics	155	57	212
No diuretics	454	243	697
Total	609	300	909
Percentage positive	25·5	19·0	

χ^2 test, $p<0·031$, relative risk=0·69; 95% confidence limits=0·49 to 0·97

Correspondence to J J Harding.

Table 3 *Diuretics as protective agents in older patients (aged 70–79)*

	Controls	*Cases*	*Total*
Reporting diuretics	99	27	126
No diuretics	183	110	293
Total	282	137	419
Percentage positive	35·1	19·7	

χ^2 test, $p<0·001$, relative risk=0·45; 95% confidence limits=0·28 to 0·74

Table 4 *Percentage of cases and controls reporting different diuretics*

	Present study		*Edinburgh**	
	Control	*Cases*	*Control*	*Cases*
Amiloride	3·9	3·3	2·8	3·5
Bumetanide	1·3	3·0	0·9	1·2
Bendrofluazide	3·3	1·7	4·9	6·6
Cyclopenthiazide	10·8	3·7	3·7	2·7
Frusemide	3·9	3·7	3·1	6·5
Hydrochlorthiazide	4·8	4·0	–	–
Spironolactone	1·8	4·0	–	–
Triamterene	1·2	0·7	–	–
Other	1·8	2·7	–	–

*from Clayton *et al.*[1]

Table 5 *Cyclopenthiazide as a protective factor for cataract – contingency table*

	Controls	*Cases*	*Total*
+Cyclopenthiazide	66	11	77
−Cyclopenthiazide	543	289	832
Total	609	300	909
Percentage positive	10·8	3·7	

χ^2 test, $p<0·001$; relative risk=0·31; 95% confidence limits=0·16 to 0·60

Table 6 *Spironolactone as a risk factor for cataract*

	Controls	*Cases*	*Total*
Spironolactone	11	12	23
Without spironolactone	598	288	886
Total	609	300	909
Percentage positive	1·8	4·0	

χ^2 test, $p<0·05$, relative risk=2·3, 95% confidence limits=1·002 to 5·28

attached to each. The risk associated with spironolactone is discussed under diuretics.

DIURETICS

Diuretics have been reported as a risk factor in the Edinburgh study,[1] but this did not emerge from our results. In fact diuretics appeared to provide some protection (Table 2), especially in older patients (Table 3). The imbalance between cases and controls differed for different diuretics, with an excess of cases for bumetanide and spironolactone contrasting with an excess of controls reporting bendrofluazide and cyclopenthiazide (Table 4). The Edinburgh study found excess reports of every diuretic except cyclopenthiazide in cases, whereas we found several diuretics with an excess in controls (Table 4). The age-sex distributions of our cases and controls were almost identical, whereas the Edinburgh study had an excess of older cataract patients, who would increase the score for all diuretics. We analysed the data for each diuretic by χ^2 test: only two produced significant results. Cyclopenthiazide (Navidrex K) appeared to be protective, decreasing the risk of cataract by a factor of nearly 3 (Table 5). The proportion of subjects reporting cyclopenthiazide was greater in each of the four control groups than in the cases. The only diuretic found to be a significant risk factor was spironolactone, with a relative risk of 2·3 (Table 6). This drug is a steroid, and the associated risk of cataract seems to be similar to that for the other steroids (Table 1). When subjects reporting spironolactone (a risk factor) and/or cyclopenthiazide (a protective factor) were removed from the data, patients reporting other diuretics were equally distributed between the cases (12·0%) and controls (13·0%), so that the apparent protective effect of diuretics (Table 2) was entirely due to cyclopenthiazide.

NIFEDIPINE

Nifedipine has not been mentioned as a possible risk factor for cataract but it appeared to be so in our study (Table 7). The cases reporting nifedipine had no striking common feature except as expected for angina (5 out of 9) and hypertension (8 out of 9). This risk may be related to hypertension, which others have reported as a risk factor.[1]

CIGARETTES

Subjects were asked about their past and present use of cigarettes and number of years as a smoker. Daily cigarette consumption multiplied by years as a smoker gave a cigarette-year value which was used to group subjects. The highest group was more common among cases, and so a contingency table was drawn up comparing these 'heavy smokers' – that is, those whose cigarette-year score exceeded 1500 – with non-smokers (Table 8). Only 2·8% of the controls reported this level of smoking compared with 7% of cases. By our definition 'heavy smoking' of cigarettes was associated with a doubling of the risk of cataract. A similar increase was reported from Edinburgh.[1]

Table 7 *Nifedipine as a risk factor for cataract*

	Controls	*Cases*	*Total*
Nifedipine	7	9	16
Without nifedipine	602	291	893
Total	609	300	909
Percentage positive	1·2	3·0	

χ^2 test, $p<0·05$; relative risk=2·7, 95% confidence limits=1 00 to 7·32.

Table 8 *Cigarette smoking and cataract*

	Controls	*Cases*	*Total*
'Heavy smoker'*	25	21	46
Non-smoker	241	103	344
Total	266	124	390
Percentage positive†	2 8	7·0	

χ^2 test, $p=0·032$; relative risk=1·97, 95% confidence limits=1·05 to 3·67.

*'Heavy smoker' means subjects with cigarette-year score >1500—e g subject who smoked more than 30 cigarettes/day for 50 years or 40 cigarettes/day for 37 5 years, etc

†Percentage of the total in the study.

Table 9 *Beer drinking and cataract*

	Controls	*Cases*	*Total*
More than 2 pints/day	15	15	30
Nil to 2 pints/day	594	285	879
Total	609	300	909
Percentage 'heavy'	2 5	5·0	

χ^2 test, $p=0·044$; relative risk=2 08; 95% confidence limits=1 005 to 4·32.

2 Pints=1136 ml.

Table 10 *Contingency table for aspirin as a possible protective agent against cataract*

	Controls	*Cases*	*Total*
Aspirin	44	15	59
No aspirin	565	285	850
Total	609	300	909
Percentage positive	7 2	5·0	

χ^2 test, $p=0·2$, not significant.

Table 11 *Paracetamol (acetaminophen) as a protective factor against cataract—contingency table*

	Controls	*Cases*	*Total*
Paracetamol	107	26	133
No paracetamol	502	274	776
Total	609	300	909
Percentage positive	17·6	8·7	

χ^2 test, $p<0 001$, relative risk=0·45, 95% confidence limits=0·29 to 0 71.

Table 12 *Aspirin-like analgesics as protective factors against cataract*

	Controls	*Cases*	*Total*
Aspirin-like analgesics	185	51	236
No aspirin-like analgesics	424	249	673
Total	609	300	909
Percentage positive	30 4	17·0	

χ^2 test, $p\ll0·001$; relative risk=0·47; 95% confidence limits=0·33 to 0·66.

ALCOHOL

Subjects were asked about their consumption of beer, wines, and spirits separately. The score for all three was added to give a total alcohol score. Those reporting higher scores for total alcohol, past and present, were overrepresented among cases, indicating a possible risk, but comparison of those consuming 10 or more units of alcohol per day with those consuming less did not reveal a significant difference by the χ^2 test (one unit of alcohol is half a pint (284 ml) of beer, or one glass of wine, or a single whisky). For individual beverages 'heavy drinkers' (more than 4 units per day) of either spirits or beer were overrepresented among cases. The difference for spirits was not statistically significant, but 'heavy' beer drinkers appeared to double their risk of cataract (Table 9). The cataract group had a greater proportion of subjects reporting a high beer consumption than any of the four control groups. All but one of the 'heavy' beer drinkers were male, and in males alone the risk was similar to the overall risk: relative risk=2·2 (95% confidence limits 1·02 to 4·66), $p=0·041$. An association between cataract and high alcohol consumption was reported by Clayton *et al.*[1]

ASPIRIN-LIKE ANALGESICS: PROTECTIVE FACTORS?

Risk factors are those factors experienced by a significantly greater proportion of cases than of controls. To our surprise some drugs were reported by a greater proportion of controls than of cataract patients, indicating a possible anticataract effect. These drugs were the aspirin-like analgesics (non-narcotic analgesics). Aspirin was reported by 7·2% of controls and 5·0% of cases, but this difference was not statistically significant (Table 10). Paracetamol (acetaminophen) was reported by twice as many controls as cases and emerged as a highly significant protective factor, with a relative risk of 0·45 (Table 11). The 95% confidence limits for this relative risk are 0·29 to 0·71. Consumption of paracetamol for at least four months is associated with a significant protection against cataract. The proportion of subjects reporting other aspirin-like analgesics was also greater among controls than cases, so we analysed

Table 13 *Protection by aspirin-like analgesics in those not reporting steroids*

	Controls	*Cases*	*Total*
Aspirin-like analgesics	172	42	214
No aspirin-like analgesics	399	226	625
Total	571	268	839
Percentage positive	30·1	15·7	

χ^2 test, p<<0·001, relative risk=0·43, 95% confidence limits=0·30 to 0·63.

the data for these drugs as a whole (Table 12). The relative risk was very similar for the entire group, again indicating that either taking aspirin-like analgesics or something closely associated with taking these analgesics had halved the risk of cataract. The extent of protection was very similar in males and females.[4] The term 'aspirin-like analgesics' includes aspirin, paracetamol, ibuprofen and similar drugs, naproxen, benorylate, mefenamic acid, and flufenamic acid. The proportions of total controls reporting these drugs were 7·2% aspirin, 17·6% paracetamol, 7·2% ibuprofen family, 4·1% for the rest.

As the implications of the association between these drugs and protection against cataract are so important, it is necessary to be sure that the association is real. It is useful therefore to compare the different control groups lest the result be due to a single group, perhaps the hospital controls, being major consumers of analgesics. In fact aspirin-like analgesics were reported by 29·9%, 32·1%, 32·3%, and 27·0% of the hospital controls and three community control groups respectively compared with only 17% of cataract patients.[4] The close comparability of the four different control groups, all of them differing widely from the cases, enhances our confidence that the association between aspirin-like analgesics and protection against cataract is real. The low p value adds further support to that view. Many of the subjects reporting aspirin-like analgesics also reported arthritis (42% of cases and 36% of controls), and some of these had also reported taking steroids, a known risk factor for cataract in our population (Table 1). It seemed useful therefore to exclude those reporting steroids from the analysis. On doing so the apparent protection by aspirin-like analgesics increased slightly (Table 13). The apparent protection by paracetamol increased slightly, remaining highly significant (Table 14). Without the steroid takers ibuprofen emerged as a significant protective factor (Table 15).

Table 14 *Protection by paracetamol in those not reporting steroids*

	Controls	*Cases*	*Total*
Paracetamol	100	22	122
No paracetamol	471	246	717
Total	571	268	839
Percentage positive	17·5	8·2	

χ^2 test, p<0·001, relative risk=0·42; 95% confidence limits=0·26 to 0·68

Table 15 *Protection by ibuprofen in those not reporting steroids*

	Controls	*Cases*	*Total*
Ibuprofen	40	8	48
No ibuprofen	531	260	791
Total	571	268	839
Percentage positive	7·0	3·1	

χ^2 test, p<0·025, relative risk=0·41, 95% confidence limits=0·19 to 0·89

Discussion

It appears from these results that a variety of drugs affect lens opacification but most surprisingly that some, the aspirin-like analgesics, may exert a protective effect. We did not attempt to validate drug consumption. The usual method by blood and urine tests is not possible, because our interest extended to drugs taken in the past. Validation from hospital notes or general practitioner notes would not be useful, as they are not comparable, and some drugs that were most interesting are over-the-counter drugs. However, most patients seem confident in remembering drugs they have taken regularly for at least four months, and any lack of recall should be the same in all groups. Comparisons we have made between the five groups[3] indicate that the powers of recollection of the different groups are comparable.

STEROIDS

Steroids were associated with an 80% increase in the risk of cataract. There are several ways in which steroids could cause cataract. They can increase glucose levels in plasma and aqueous humour, increase cation permeability, inhibit Na-K-ATPase and glucose 6-phosphate dehydrogenase and RNA synthesis[6] and can bind to lens proteins.[7] The steroids previously associated with cataract have a side chain structure that permits reaction with amino groups to form a stable adduct. Spironolactone does not have this side chain, but both spironolactone and prednisolone have a carbonyl function on the A ring where protein binding could occur. Prenisolone-protein adducts were identified in rat lenses opacified by incubation in prednisolone and in cataracts removed from patients who had received prolonged steroid therapy.[8]

DIURETICS

From our results we conclude that spironolactone, a steroid diuretic, is a risk factor for cataract and that other diuretics have little effect either way, except for the apparent protection by cyclopenthiazide. This contrasts with the conclusion from the Edinburgh study that all diuretics are risk factors for cataract, some worse than others, with the degree of risk related to the elevation of plasma urea.[1]

CIGARETTES AND ALCOHOL

Both 'heavy smoking' and 'heavy beer drinking' appeared as risk factors in this study (Tables 8 and 9). Cigarette smoking was the only factor where the data were stratified after all the interviews had been completed No close relationship was observed, and comparison of all smokers with non-smokers did not reveal a risk. Furthermore there is a possibility of confounding between cigarette smoking, beer drinking, and work on a military base, which was reported as a risk factor in the preceding paper,[5] but analysis for interaction between risk factors by means of GLIM (Royal Statistical Society, Edinburgh) indicated that these three risk factors are independent.

ASPIRIN-LIKE ANALGESICS: PROTECTIVE FACTORS?

The protective effects of aspirin-like analgesics (non-narcotic analgesics[9]) have been reported briefly by us,[4] but here we present the contingency tables for individual members of this family. Earlier studies indicating that aspirin protected against cataract in rheumatoid arthritis and diabetic patients[10 11] were criticised.[12] Subsequently we showed that aspirin could prevent the cyanate-induced opacification of incubated rat lenses.[13] The strong association between consumption of aspirin, paracetamol, ibuprofen, and similar drugs and protection against cataract in this study does not establish a causal relationship, but if these drugs are not responsible for the protective effect it means that those subjects taking them are protected in some other way, perhaps by the condition for which they took the drugs. However, the drugs were taken for a variety of reasons—about 40% for arthritis. It seems unlikely that arthritis protects against cataract, and it would have to be an extremely powerful effect fully to explain the results, because only 36% of the controls reporting these drugs had also reported arthritis. It is no more likely that suffering pain protects against cataract. We can think of no explanation other than a direct protection against cataract by aspirin-like analgesics. Most of the standard criteria for a causal relationship[14] are satisfied in this study. The only previous link between the aspirin-like analgesics and cataract was in the studies of aspirin Before our study there was no suggestion that paracetamol, ibuprofen, and the other drugs might have any protective effect.

Various mechanisms have been proposed for the apparent protective effect of aspirin, but most recently we have favoured the view that acetylation of the lens proteins served to protect them against chemical insults such as cyanate, glucose, glucose 6-phosphate, and prednisolone that are associated with cataract.[13] This mechanism received further support from laboratory studies of Rao *et al.*[15] This explanation cannot be extended to the other aspirin-like analgesics, because most of them lack an acetyl group and therefore cannot acetylate proteins. A mechanism involving prostaglandins is superficially attractive, but paracetamol, which is a feeble inhibitor of prostaglandin synthesis, appears strongly protective against cataract, whereas indomethacin, a powerful inhibitor of prostaglandin synthesis, is not protective, being reported by 3·1% of controls and 3·3% of cases. They may act by lowering blood glucose levels.[4] Aspirin-like analgesics lower fasting blood glucose levels in diabetics and non-diabetics[16 17] and improve glucose tolerance[16 18 19] and the insulin response to glucose.[17 19] These properties are shared by aspirin, salicylates, and ibuprofen but not by indomethacin [20-22]

If aspirin-like analgesics are protective because they lower blood glucose, it would imply that the level in many subjects aged 50 to 79 is higher than is healthy for the lens. There is some evidence to support that notion. First, diabetes is such a powerful risk factor[3] that any elevation of blood glucose could be harmful Indeed, it was shown in the Edinburgh survey that the mean glucose level in cataract patients exceeded that of controls even when diabetics were excluded from the analysis.[23] Secondly, it has been reported that 44% of cataract patients have an abnormal glucose tolerance curve.[24] A moderate but chronic elevation of glucose concentration is unlikely to have any osmotic effect and is more likely to act through non-enzymic glycosylation of lens proteins. This reaction occurs to most proteins, notably to long-lived proteins found in the tissues that are damaged in diabetes.[25] If the aspirin-like analgesics protect against cataract by lowering blood glucose levels, it is possible that they give some protection against other glucose-induced damage—perhaps retinopathy, neuropathy, and basement membrane damage. An apparent protection by aspirin against diabetic retinopathy has been noted.[26 27]

A second case control study in Oxford that incorporates more detailed questions on analgesics has been started so that the dosage required of a protective effect can be elucidated. There are studies indicating that low-dose aspirin protects against myocardial infarction, unstable angina, and strokes. Additional protection against cataract would be a great bonus, although some might prefer paracetamol as a potential anticataract drug. Indeed, it is possible that paracetamol is also effective against the above life-threatening conditions.

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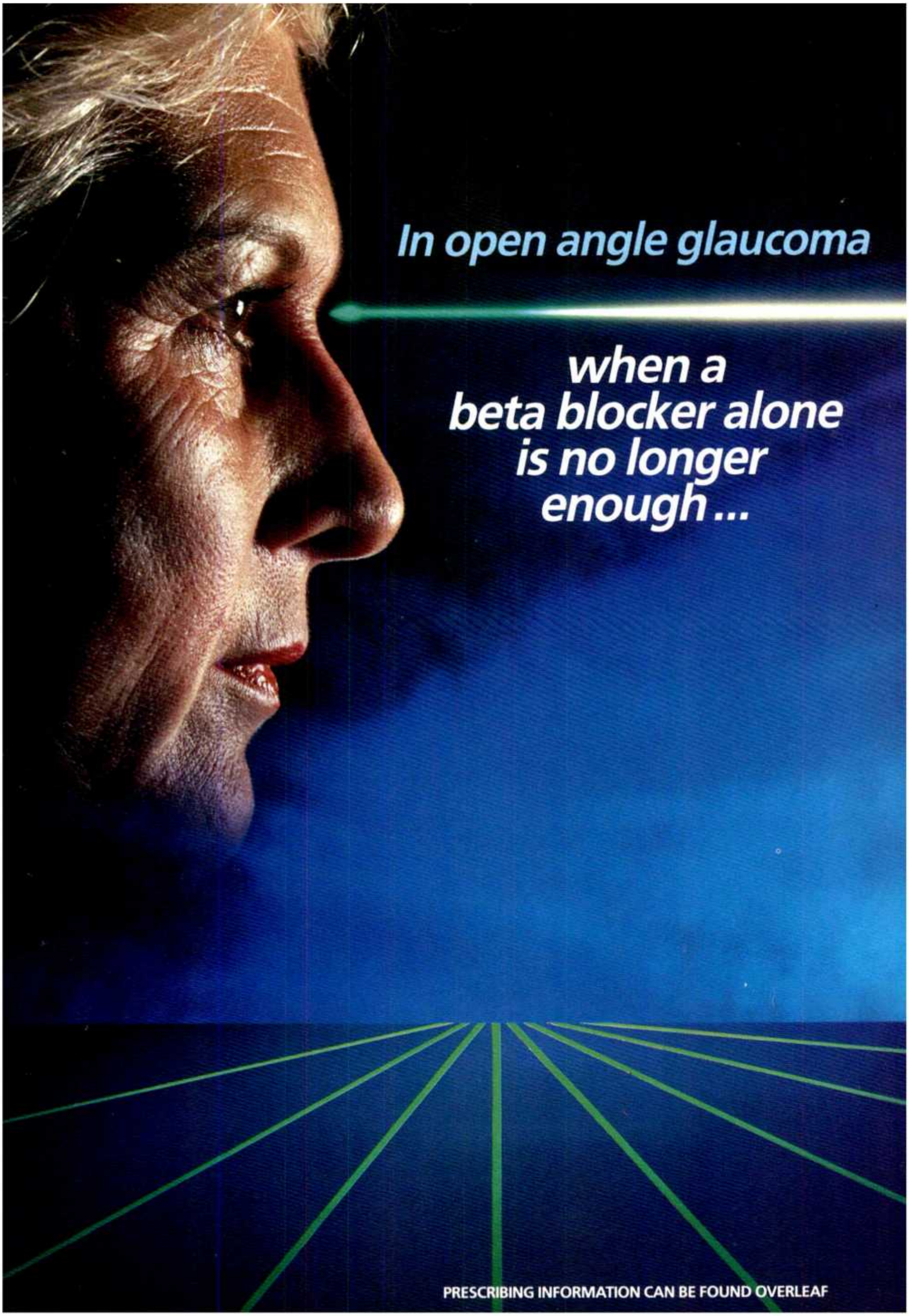
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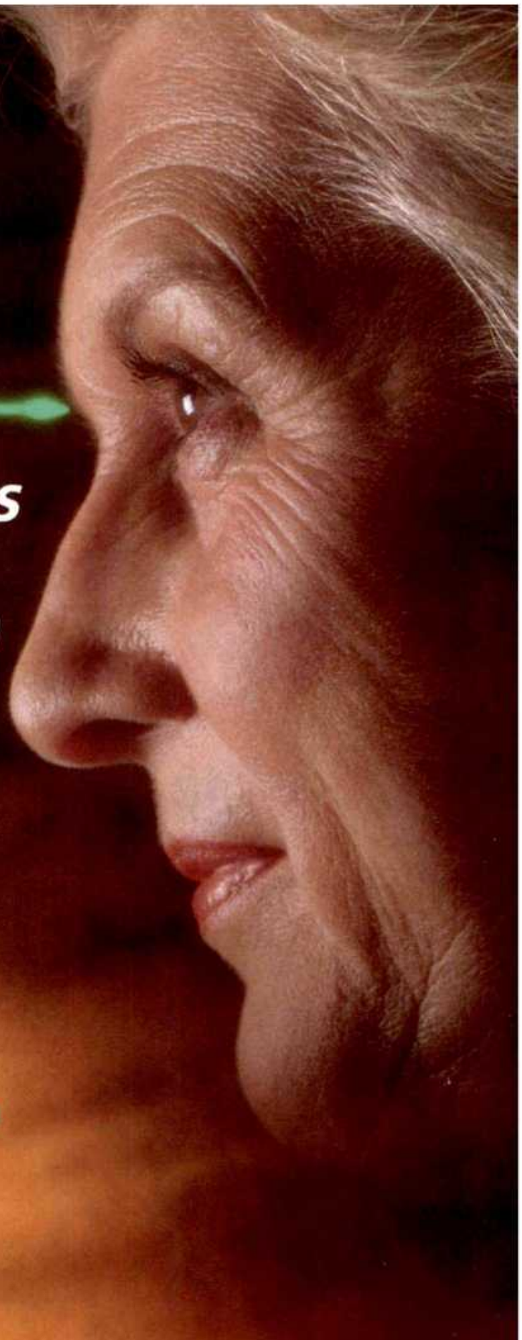

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Stabilisation of refraction following cataract surgery

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SUMMARY Refraction was performed at frequent, regular intervals for six months following routine intracapsular cataract extraction. Patients were divided into two groups, those whose limbal sections were closed with 8-0 virgin silk or with 9-0 nylon. The stabilisation of refraction was observed, and the most suitable time to prescribe 'first glasses' was estimated retrospectively. In the silk group this was found to be at three months in the nylon group at four months. However, results in the latter were less predictable with greater variation.

This report was undertaken to determine the rate of stabilisation of refraction following intracapsular cataract extraction, with the aim of improving efficiency of the 'first glasses' prescription.

Many authorities recommend prescribing glasses when serial refraction shows no significant change If this procedure is followed carefully, it may require frequent clinic visits Hence first glasses are often prescribed after a fixed postoperative period of about two months. This has been the practice for several decades, during which surgical practices and patient expectations have changed greatly.

Glasses prescribed too early, before refraction has stabilised, may cause disappointment and unnecessary expense for the patient; too late prescription may prolong disability and frustration.

Changes in corneal curvature following cataract surgery have been recognised for over a century, having been first described by Donders[1] in 1864. Many other workers have since investigated the nature of postcataract astigmatism The effects of the following factors have been studied: type,[2-4] depth,[5] and number[4] of sutures, pre- or postplaced sutures,[6] wound placement,[7] and size of wound.[8] Change of corneal curvature as a function of time has also been considered.

In 1935 Groenholm[9] reported keratometric studies on 200 eyes following cataract extraction without sutures and with one or two sutures. The initial high degree of astigmatism at 10 days was found to be halved at two months. Particular attention was paid to resultant astigmatism and frequent regular keratometry was not included.

Floyd[10] reported on a total of 47 eyes following cataract surgery with Graefe section and two sutures. Keratometry was performed at monthly intervals and he found 'significant' changes in corneal curvature, up to three months after surgery. He suggested that glasses prescribed before this time may be of a temporary nature. More recently Reading[8] reported on 43 eyes undergoing intracapsular cataract extraction sutured with virgin silk. These patients were followed up at monthly intervals for one year by photokeratometry. Changes in corneal curvation after one month were found to be 'small'.

The present study, conducted at Wolverhampton Eye Infirmary, was designed to help resolve the following questions: How quickly does refraction stabilise sufficiently to allow prescription of satisfactory glasses? Is this rate consistent in different patients? Is it influenced by the type of suture and the initial degree of corneal distortion produced during surgery?

Material and methods

PATIENTS

From the beginning of the study all patients undergoing uncomplicated cataract extraction were included provided they were able, co-operative, and had no other serious ocular disease. A total of 43 patients, 47 eyes (average age 70 years, range 49–86 years, 95% confidence interval 2·8) were followed up for six months.

SURGERY

Five different surgeons performed the operations using a similar microsurgical technique: ab externa stepped incision (approx 160°) followed by one peripheral iridectomy and irrigation with α-

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chymotrypsin. Intracapsular cataract extraction was then performed with a cryoprobe. The wounds were closed either by interrupted 8-0 virgin silk (5–7 sutures) or by a double 9-0 nylon bootlace (each one closing half the wound, giving a total of six bites). The choice of suture alternated between patients; 24 eyes were closed with virgin silk, 23 eyes with nylon. A total of 15 eyes had iris clip intraocular lenses inserted (Binkhorst or Boberg-Ans types), nine in the virgin silk group and six in the nylon group. All patients were prescribed a topical steroid (betamethasone 0·1%), four times a day for four weeks; this was then reduced and discontinued over the following two weeks.

FOLLOW-UP

All patients were followed up by the author for six months. Keratometry was performed preoperatively and in the first week following surgery along with the first refraction. Refraction was repeated at two-weekly intervals for three months, thereafter monthly for three further months.

Keratometry was performed on a Bausch-Lomb keratometer. All refraction was carried out with the same equipment, ensuring constant back vertex distance. Retinoscopy was followed by subjective refraction, the sphere confirmed by the duochrome test and the cylinder and axis by using Jackson's cross cylinder.

Analysis of the data was by either independent or paired t test with 95% confidence intervals and χ^2 tests. Pearson product moment correlations were also computed to investigate the relationship between certain variables.

Results

To display best the speed at which refraction stabilised after intracapsular cataract surgery the rate of change of each component, namely sphere, cylinder, and axis, was calculated from each patient's serial refractions. The units of change were dioptres/week and degrees/week. The mean values are shown in Fig. 1 for the two suture groups, 8-0 virgin silk and 9-0 nylon.

Virgin silk sutures tend to lose their apparent strength in the second month after surgery. This shows itself by a sudden change in cylinder from with the rule to against the rule.[11] In this study, six months after operation, significantly more of the silk group had a cylinder against the rule, 22 (92%), as opposed to 4 (17%) of the nylon group, ($\chi^2=23\cdot3$, $p<0\cdot001$).

Fig. 1C shows this dramatic change taking place in the first two months (that is, a peak in the rate of change of axis), but thereafter the rate of change remained low. Both suture groups showed significant changes in all three components of refraction for at least the first three months.

In each graph the nylon suture curve shows a more gradual change which is also slightly more prolonged. The different shapes of the curves for the two suture groups are reflected in the differing 'prescribing times'. This was taken to be the time, following surgery, that the refraction was judged to be stable enough to allow prescription of satisfactory glasses. For the purposes of this study the prescribing time was estimated retrospectively when all the refraction results for the full six months were reviewed. The

Fig. 1 *Comparison of the rate of change of each component of refraction in the two suture groups of interrupted 8-0 virgin silk and continuous 9-0 nylon, against time following intracapsular extraction.*

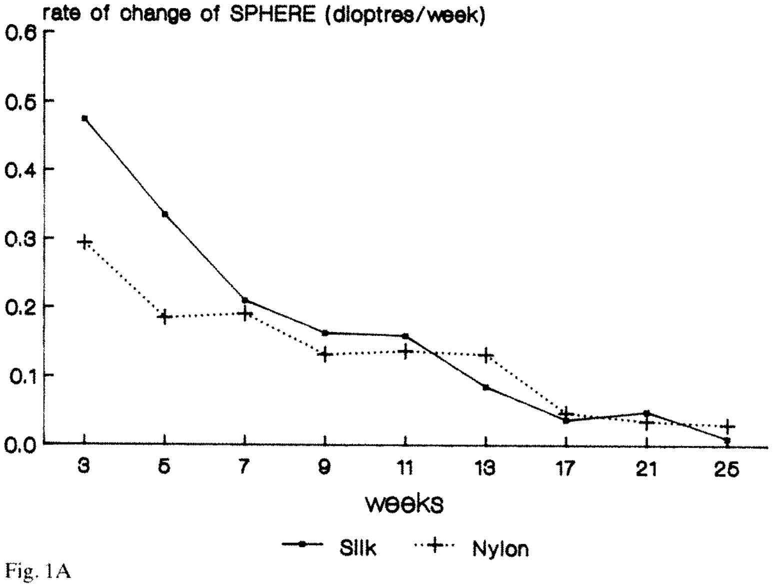

Fig. 1A

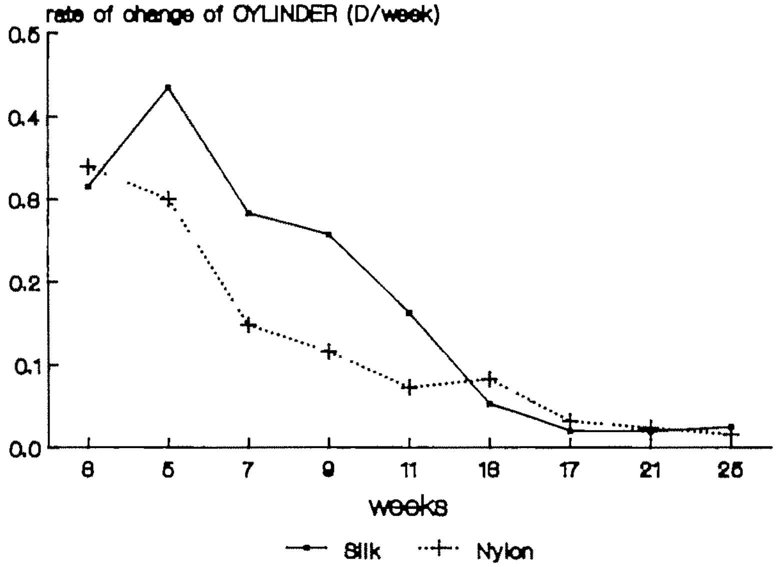

Fig. 1B

prescribing time was taken to be the earliest time that refraction approached the 'final' six-month result. The criteria used was a maximum difference of 0·5 dioptres in sphere, 0·25 D in cylinder, and 5° in axis.

The results are displayed in Fig. 2, which shows when the patients reached a stable refraction.

Statistical comparison of the mean prescribing time showed a significant difference between the two suture groups, ($t_{45}=2{\cdot}18$, $p<0{\cdot}05$; mean difference= 2·3 weeks) (Table 1).

In each suture group there was no significant difference in prescribing times of eyes with and without intraocular lenses. Silk group mean difference with and without IOL=0·089 weeks (95% CI±2·05); nylon group mean difference=2·45 weeks (95% CI±4·21).

Pre- and postoperative keratometry was performed to estimate the degree of corneal distortion caused by the incision and sutures. The maximum change occurred about the vertical axis. This change,

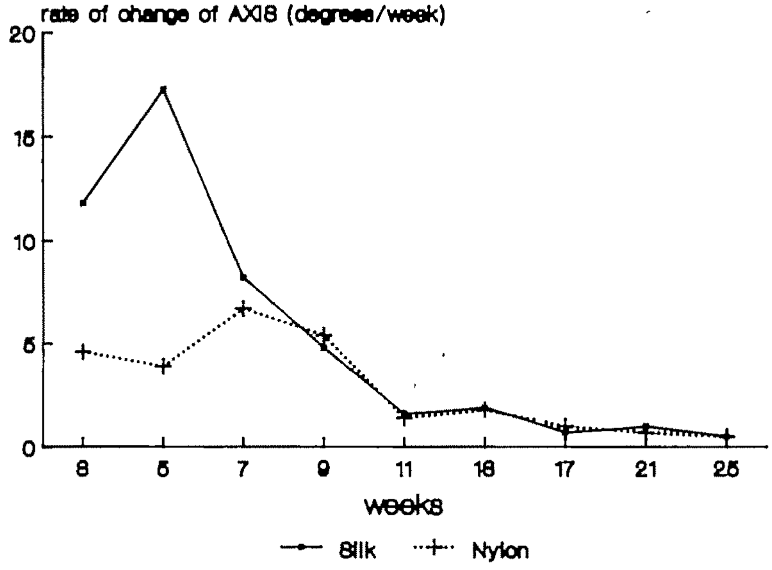

Fig. 1C

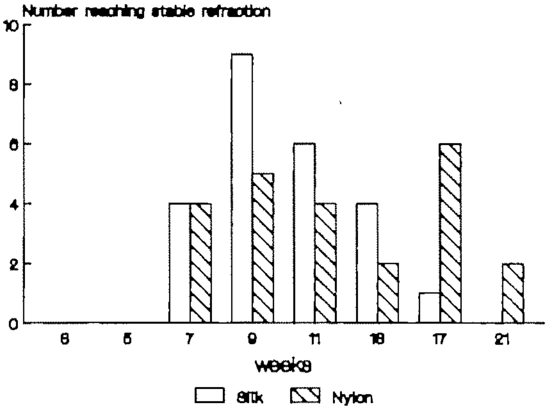

Fig. 2 *Comparison of the rate of stabilisation of refraction in the two suture groups of interrupted 8-0 virgin silk and continuous 9-0 nylon, as measured by the time first glasses could be prescribed following intracapsular extraction*

Table 2 *Comparison of surgical corneal distortion and initial and final astigmatism following intracapsular extraction sutured with interrupted 8-0 virgin silk or 9-0 continuous nylon*

	Suture material	
	8-0 Silk	*9-0 Nylon*
No. of eyes	24	23
Mean corneal distortion	2 75 D (±0 66)*	3 36 D (±0·74)
Mean initial cylinder, 1st week	1 84 D (±0 41)	2 69 D (±1·1)
Mean final cylinder, 6th month	2 13 D (±0 39)	1·58 D (±0 38)
Mean initial axis	100 4° (±10 5)	98 9° (±6 6)
Mean final axis	174 4° (±16 5)	117° (±20)
Mean prescribing time, 1st glasses	10 2 weeks (±1 0)	12 5 weeks (±1 9)

*95% confidence interval in parentheses

measured in dioptres, was used as an estimate of surgically induced corneal distortion. This is shown in Table 2 with the initial (1st week) and final (6th month) cylinder and axis for comparison. Correlation analysis was performed to investigate their relationship (Table 3).

Discussion

The two different suture techniques, for intracapsular cataract extraction, examined in this study (interrupted 8-0 virgin silk and continuous 9-0 nylon) appear to have different effects on the course of postoperative refraction and its rate of stabilisation Once stable, 22 (92%) of the silk group have a cylinder (mean 2·13 D) against the rule, and 19 (83%) of the nylon group remain with a cylinder (mean 1·58 D) with the rule.

As can be seen from Table 3, in the silk group there was no significant relationship between the initial corneal distortion and the time that the postoperative refraction was considered stable enough to prescribe first glasses ('prescribing time'). The initial corneal distortion is dependent on the positioning and tension of the sutures. But as silk loses its apparent strength in four to six weeks,[12] the initial distortion can be expected to have little correlation with the prescribing time and the final degree of cylinder. The loss of tension in the silk suture results in a dramatic change in cylinder, as shown in Fig. 1.

In the nylon group the relationship between initial corneal distortion and prescribing time was significant, that is, eyes with most distortion take longest to stabilise. Nylon sutures lose their tensile strength very gradually and cause less adjacent tissue reaction. Hence the initial distortion caused by the suture will influence the behaviour of the wound for a longer period of time than silk. The limbal tissue adjacent to the suture may undergo a certain degree of moulding, and the suture itself may cheese-wire through the tissue slightly. These effects would allow a reduction and equalisation of the tension across the wound. Hence one may expect the amount of

Table 1 *Comparison of first glasses 'prescribing time', following intracapsular extraction, between wounds closed with interrupted 8-0 virgin silk and continuous 9-0 nylon sutures*

	Suture material	
	8-0 Silk	*9-0 Nylon*
No of eyes	24	23
Mean prescribing time (weeks after surgery)	10·2	12·5
95% CI	±1 0 (9 2–11 2 weeks)	±1 9 (10 6–14 4 weeks)

CI=confidence interval

Table 3 *Correlation analysis of the relationship between the degree of initial surgical corneal distortion, final cylinder, and 'prescribing time', in the two suture groups of interrupted 8-0 virgin silk and continuous 9-0 nylon*

	Suture material	
	8-0 Silk	*9-0 Nylon*
Initial distortion *v* prescribing time	r_{22}=0 02	r_{21}=0 41
Initial distortion *v* final cylinder	r_{22}=0 11	r_{21}=0 12
Final cylinder *v* prescribing time	r_{22}=0 39	r_{21}=−0 21

cylinder to lessen before the wound has stabilised fully. This appears to be the case in the nylon group, as the mean initial cylinder of 2·69 D (axis 98·9°) reduces to 1·58 D (axis 117°) at six months. A similar result was found by Wyman,[3] who followed up 100 cases sutured with 9-0 and 10-0 nylon

The relationship between final cylinder and prescribing time shows an interesting difference between the two suture groups. It suggests that the eyes with longer prescribing times have wounds which take longer to reach sufficient strength to stabilise refraction. Before reaching this point the refraction can be influenced by the changing tensions or effective loss of sutures. In the silk group the longer prescribing times are associated with a larger final cylinder (92% against the rule), that is, more time for stretching of the wound before it reaches sufficient strength to become stable In the nylon group the longer prescribing times are associated with a smaller final cylinder (83% with the rule), that is, more time for stretching of the sutures and moulding of adjacent limbal tissue. In this study there was no significant relationship in either suture group between the initial corneal distortion and the amount of final cylinder.

Of particular interest was the rate at which refraction stabilised sufficiently to allow prescription of first glasses. Here there was a significant difference between the nylon and silk suture groups. The mean prescribing time in the silk group was 10·2 weeks (95% CI±1·0); in the nylon suture group not only was the mean prescribing time later at 12·5 weeks (95% CI±1·9) but also the spread was greater.

In absolute terms only 13 (54%) of the silk suture group were considered sufficiently stable to prescribe first glasses at the traditional postoperative period of two months. This reached 23 (96%) at three months and 24 (100%) at four months. In the nylon suture group nine (39%) were stable at two months, 15 (65%) at three months, 21 (91%) at four months, and 23 (100%) at five months.

In summary, three months would appear to be a practical time to refract and order glasses for patients whose eyes have been sutured with virgin silk. This should improve efficiency and avoid multiple refractions in the great majority of patients. However, when an eye has been sutured with continuous nylon, the stabilisation is less predictable and more caution is required. It may be reasonable to wait four months before ordering first glasses. However, after the third month the changes were fairly predictable: 87% showed a slight drop in the amount of cylinder of up to 0·75 dioptres, with only small changes in axis. Hence, if it is necessary to prescribe glasses earlier, a slightly smaller cylinder than indicated could be given.

Limbal wounds closed by sutures or techniques different from above,[4,11] such as interrupted 10-0 nylon, may well respond differently, and the smaller sections used in extracapsular cataract surgery, particularly phacoemulsification, can be expected to have less effect on postoperative refraction. However, it is unlikely that the large sections of intracapsular surgery, if closed by a different technique, would stabilise any quicker, as the speed of wound healing, which is a major factor, would remain largely unchanged.

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Surgery of aphakic retinal detachment

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SUMMARY In a prospective study 84 patients with aphakic retinal detachment were treated either by local scleral buckling alone or combined with an encirclement. The rate of surgical reattachment of the retina was found to be similar with either technique over a minimum follow-up period of one year. Simplicity and a low incidence of serious complications of the local procedure merit its application as the initial method of repairing aphakic detachments.

About 20% of all retinal detachments occur in aphakic eyes.[1] Vitreous complications associated with the removal of cataract as well as other factors like myopia and lattice degeneration predispose the aphakic eye to an early retinal detachment.[2] Preservation of the integrity of the posterior segment by performing extracapsular cataract surgery is being popularised in order to reduce the incidence of aphakic retinal detachment.[2]

The surgery of aphakic retinal detachment (ARD) is considered to be relatively difficult because of its rapid progression to total separation and an increased tendency to develop proliferative vitreoretinopathy quickly.[3] Moreover, small oral or postoral retinal holes are said to be common and can be easily missed.[4] It is therefore often argued that the surgery of aphakic retinal detachment should preferably include an encirclement procedure. However, an encircling element carries certain specific disadvantages, and its absolute necessity has never been clearly established.[5]

The significance of cerclage was therefore studied in a series of aphakic retinal detachments, and the results are reported here.

Materials and methods

All consecutive aphakic retinal detachments occurring in patients above 40 years of age were thoroughly examined for surgical repair, and cases for the present study were carefully selected in conformity with the following criteria: (1) good pupillary dilatation and clear optical media; (2) separated retina fairly mobile, with absent or minimal periretinal fibrosis; (3) if multiple, all retinal breaks localised to one quadrant of the fundus only; (4) no contraindication to the patient's receiving repeated general anaesthetics; (5) no previous retinal detachment surgery to the affected eye.

Cases with similar retinal detachments as regards the type of retinal break and extent of retinal separation were allocated alternately to group A and group B. Forty eyes in group A received only localised buckling with Silastic sponges or silicon tyres as explants. Forty-four eyes in group B, however, were also given an encerclage with a 2·5 mm wide silicon rubber band in addition to local buckling. The unequal numbers in the two groups resulted from the fact that two cases which were allocated to group A inadvertently had the group B procedure performed on them. The error was detected only at the final analysis. Therefore they had to be counted as group B. Retinal breaks were treated by cryosurgery under visual control. Drainage of subretinal fluid was avoided if possible. If it was found necessary, intravitreal air was injected to achieve near normal intraocular pressure at the end of surgery. Whenever air was injected, positioning of the patient was continued for 48 hours postoperatively. All patients were operated upon under a general anaesthetic. Most of the cases could be discharged by the fifth postoperative day. The patients were periodically reviewed for at least one year. Success was defined as reattachment of the retina for six months following the last procedure.

Results

A total of 84 cases operated upon were followed up for one to three years, average 15·5 months. Forty

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Table 1 *Extent of retinal separation at the time of surgery in each group*

	Group A	*Group B*
One quadrant	3 (7·5%)	3 (6·8%)
Two quadrants	7 (17·5%)	7 (15·9%)
Three quadrants	14 (35%)	16 (36·4%)
Four quadrants	16 (40%)	18 (41%)
Total	40	44

Table 2 *Characteristics of retinal breaks in each group*

	Group A	*Group B*
Traction tears		
Single	20 (50%)	23 (52·2%)
Multiple	2 (5%)	3 (6·8%)
Round holes		
Single	6 (15%)	5 (11·4%)
Multiple	12 (30%)	13 (29·6%)
Total	40	44

Table 3 *Results of surgery in the two groups*

	Group A	*Group B*
Success	36 (90%)	40 (91%)
Failure	4 (10%)	4 (9%)

Table 4 *Comparison of visual recovery following surgery in each group*

Visual acuity	*Group A*		*Group B*	
	Preop	*Postop*	*Preop*	*Postop*
6/6–6/12	2 (5%)	14 (35%)	3 (6·8%)	10 (22·7%)
6/18–6/36	7 (17·5%)	15 (37·5%)	6 (13·6%)	16 (36·3%)
6/60 or less	31 (77·5%)	11 (27·5%)	35 (79·6%)	18 (41%)

Table 5 *Comparison of surgical complications*

Complication	*Group A*	*Group B*
Glaucoma	–	3 (6·8%)
Anterior segment ischaemia	–	1 (2·2%)
Macular pucker	2 (5%)	4 (9%)
Choroidal detachment	1 (2·5%)	7 (15·9%)
Choroidal haemorrhage	4 (10%)	2 (4·5%)
Massive proliferative vitreoretinopathy	3 (7·5%)	5 (11·3%)

eyes in group A and 44 eyes in group B were available for analysis after a minimum follow-up of one year.

The peak incidence of ARD was seen in the 50–60 year age group. Two-thirds of the patients in each group were male. 75% of patients in this study presented within one month of experiencing the first symptom of ARD. About 25% of them were seen within two weeks.

TYPES OF APHAKIA

Eighty two patients in this series had undergone intracapsular cataract extraction and one of them had received an angle supported anterior chamber intraocular lens. In two cases an extracapsular cataract extraction had been performed. In one of them a posterior chamber intraocular lens had been implanted six months previously but vitreous had come forward through a break in the posterior capsule.

EXTENT OF RETINAL DETACHMENT

Most patients with ARD (75%) had three or all four quadrants of the fundus involved by the time these were discovered (Table 1). The extent of the detachment did not correlate well with its duration in this analysis ($p > 0.05$). ARD localised to one quadrant alone was rather rare.

RETINAL BREAKS

65% of eyes in group A and 63·7% of eyes in group B had only one retinal break. Most of these (50%) were traction tears with small triangular or typical horseshoe configuration. Single, round atrophic retinal holes were not common in this series (Table 2) In contrast, multiple round holes were more commonly encountered, accounting for 30% of ARD in group A and 29·6% of ARD in group B (Table 2). Lattice retinal degeneration, which was more frequently associated with round retinal breaks, was present in about 30% of eyes in each group.

RESULTS OF SURGERY

The anatomical results of surgery in both groups of ARD were almost similar (Table 3). After a minimum follow-up of one year, the retina remained flat in 90% of eyes in group A and in 91% of eyes in group B following the first operation.

Visual recovery was a little better in group A (Table 4). However, the difference was not significant statistically ($p > 0{\cdot}05$)

A relatively greater frequency of certain complications in group B was interesting (Table 5) Three cases of postsurgical glaucoma in group B required timolol drops 0·5% twice daily for adequate control Macular complications resulted in reduced visual outcome

Discussion

The surgical outcome of retinal detachment in an aphakic eye is generally considered to be worse than in a phakic eye[1-4] Difficulty in locating the small peripheral retinal holes in the presence of a poorly dilating pupil and hazy optical media is thought to be responsible for more operative failures.[7] Pre-existing proliferative vitreoretinopathy, or its development postoperatively, is another factor contributing to poor results of surgery for ARD[7]

Aphakic retinal detachments have been treated mostly by local scleral buckling combined with an encirclement in the hope that missed retinal holes would remain peripheral to the new ora serrata and that the subsequent development of fresh retinal breaks would not produce retinal detachment posterior to the circumferential ridge.[8] The early use of constricting encircling elements had two main objectives: the indentation of the sclera, creating a permanent buckle, and compensation for lost intraocular volume after drainage of subretinal fluid.[5] It has also been argued that an encerclage would have a permanent effect on the release of vitreous traction.[8] However, scleral buckling and the relief of ordinary dynamic vitreous traction need not to be permanent.[9]

In this study the majority of detachments were caused by a single retinal break which could be easily closed by local scleral buckling. 50% of the single retinal breaks were traction tears, which are said to be uncommon in ARD.[10] Multiple holes, widely separated in the detached retina, were rarely encountered. Similar observations have been previously reported[2] and do not support the common concept of so-called typical aphakic detachment[1] characterised by multiple holes. The success rate of reattachment with local buckling was as good as with the encirclement procedure in this study, which suggests that most ARD can be safely treated by local scleral buckling alone. A slightly better visual outcome and a low incidence of serious complications associated with local buckling, as seen in the present series, merit the application of this procedure as the initial method of repairing an aphakic retinal detachment. In this study cases of ARD with marked proliferative vitreoretinopathy and without any detectable retinal break were not included, as such eyes are usually treated by an encirclement procedure and constitute not more than 20% of all ARD cases seen in this department. Encirclement does not seem to prevent the development of proliferative vitreoretinopathy.[5]

Encirclement is a perpetuation of a tradition in retinal detachment surgery, and there has been a tendency to perform this procedure in 'difficult' cases, including aphakic detachments. Higher incidence of glaucoma, anterior segment ischaemia, and choroidal detachment in cases treated by an encirclement is well known[10] and is supported by this study. Constrictive cerclage causes undesirable radial folds, postoperative pain, induced myopia, and predisposes to late intrusion of the element.[1]

This prospective study has shown that local scleral buckling alone can be very effective in the management of the great majority of cases of aphakic retinal detachment provided a painstaking preoperative examination is carried out to locate the retinal breaks and assess the subtle vitreoretinal pathology.

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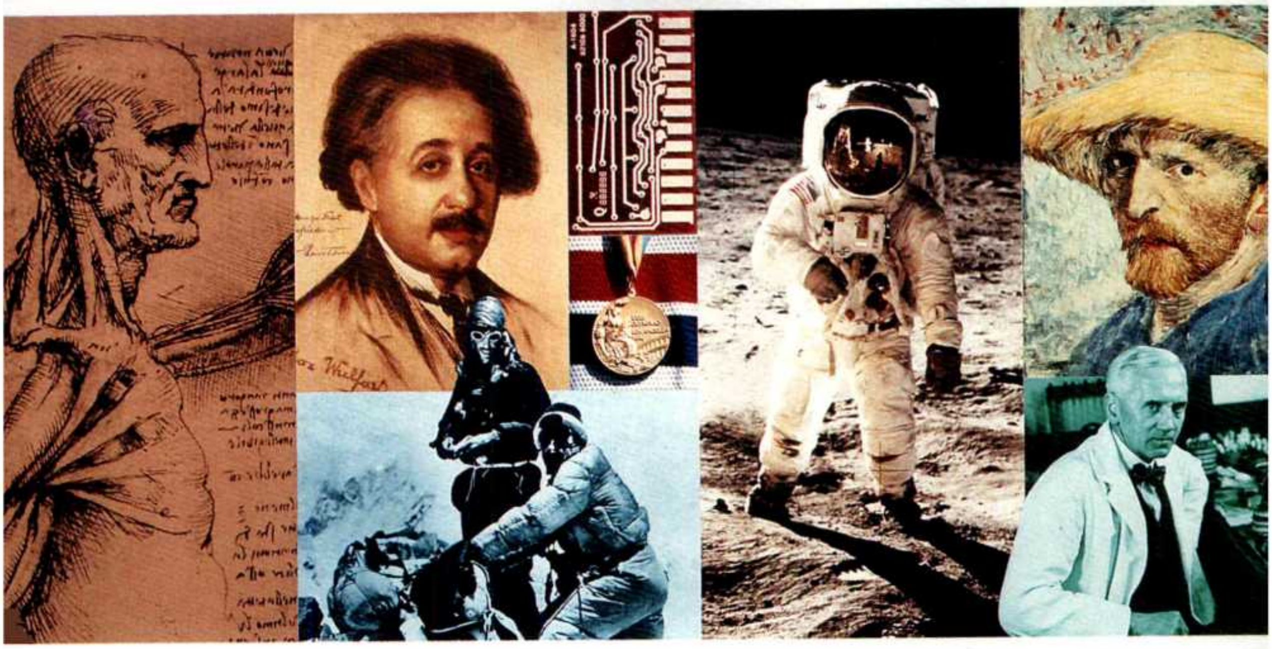

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British Journal of Ophthalmology, 1988, **72**, 823–828

Visual after-effects associated with the use of high-resolution visual display units

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SUMMARY A long-lasting visual after-effect associated with the use of a high-resolution green visual display unit (VDU) is described in eight normal volunteers. Its duration to a standard VDU exposure is measured. It is related to the McCollough effect and is thought to be either a fatiguing of green colour-coded edge-detectors or an associative phenomenon. A reduction or loss of the usual foveal peak of the critical flicker frequency (CFF) to red is also described.

We report a long-lasting visual after-effect associated with the use of a high-resolution green computer screen. In recent years there has been concern over possible hazards from exposure to television screens and more recently microcomputer monitors and visual display units (from now on collectively referred to as VDUs).[1-3] In the past, subjective visual problems with VDUs have been attributed to poor hardware design, occult refractive error, and extraocular muscle imbalance or poor working environment. Although steps have been taken to minimise these problems, one look at a microcomputer peripherals catalogue will show that they have not disappeared.[4]

There have been no scientific reports of detectable visual ill effects from VDU exposure, and it has been said that screening for such ill effects is therefore unnecessary.[1 5] The effect which we report, although not easy to quantify, is very easy to produce. We have tested eight normal volunteers for this effect. Our aims were: (1) to develop a test-card which would allow subjective detection of the after-effect; (2) to see what proportion of subjects could detect the after-effect; (3) to measure the duration of the after-effect to a standard VDU exposure; (4) to determine if there were any other effects of the green-screen VDU on colour vision.

Materials and methods

Eight normal volunteers were tested, four males and four females, with an age range of 19 to 31 and a mean age of 25. Of the eight subjects tested only one had any knowledge of the possible after-effects. No concurrent medication was allowed.

A test card was constructed (Fig. 1). This was made from a sheet of black card cut to the same size as the VDU screen. White instant lettering in various sizes (24, 18, 14, 10, and 6 point) was used for the white-on-black text, and a small section of standard typewritten text used for the black-on-white. Instant print white lines were used for the gratings (1·5 point) and the fan (2 point). The board was given a coat of matt finish protective sealant. It was examined at 0·75 m under ambient lighting.

The standard exposure to the VDU screen was taken to be reading a word processing file (1164 words on six screen pages) on a 12 inch (30 cm) green high-resolution VDU at a distance of 0·75 m under ambient lighting. Each page was exposed for one minute (extra time was spent rereading), giving a total of six minutes' exposure. The brightness control was set to the minimum usable level (where formatting instructions and other half-intensity characters become barely visible) and its position marked. The screen luminance was 2·2 cd m^{-2} as measured with a Gossen Mastersix Lightmeter (contact readings; angle $\Theta=0$). No adjustment to the system was allowed between testing, and in view of this the screen luminance was assumed to remain constant

The screen pixel resolution was 800×400. The mode used was 80 columns×24 rows Each 'letter-cell' (one column by one row) was an area 10×16 pixels. An 8×13 pixel central block was available for text construction. The blank border of the letter cell provided for horizontal and vertical letter spacing. Text was made up as in Fig. 2.

Each subject was asked to comment on the test

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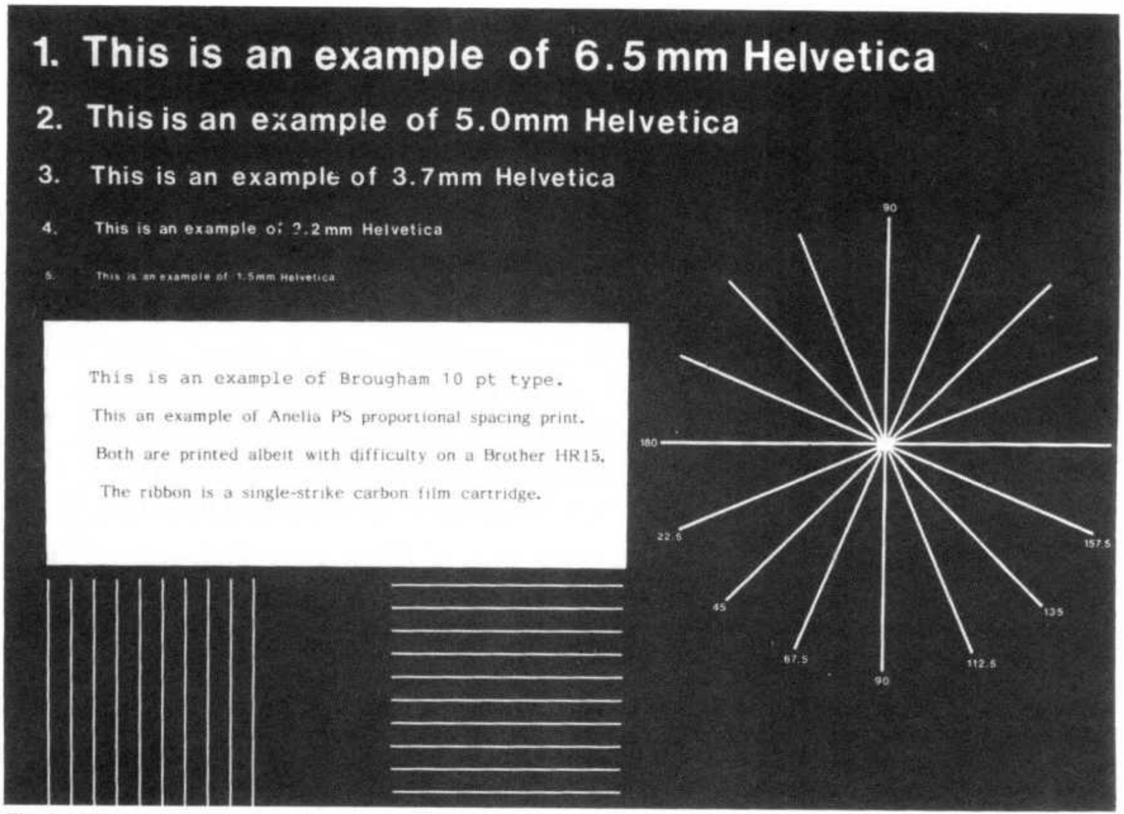

1. This is an example of 6.5 mm Helvetica

2. This is an example of 5.0mm Helvetica

3. This is an example of 3.7mm Helvetica

4. This is an example of 2.2 mm Helvetica

5. This is an example of 1.5mm Helvetica

This is an example of Brougham 10 pt type.

This an example of Anelia PS proportional spacing print.

Both are printed albeit with difficulty on a Brother HR15.

The ribbon is a single-strike carbon film cartridge.

Fig. 1 *The test card.*

card before and after VDU exposure, and then hourly thereafter until any visual after-effect had gone. Immediately after VDU exposure, but before the second test card examination, each subject was shown a plain white card. Any immediate after-image was allowed to fade completely before the second test card examination. The subjects were asked to examine and comment on the test card. A white card was then held over half the card as in Fig. 3, and the subjects again asked for their comments. Direct questions about colour were not allowed. If an after-effect was seen, direct questions were allowed about which parts of the test card were most affected.

The total duration of the effect was recorded.

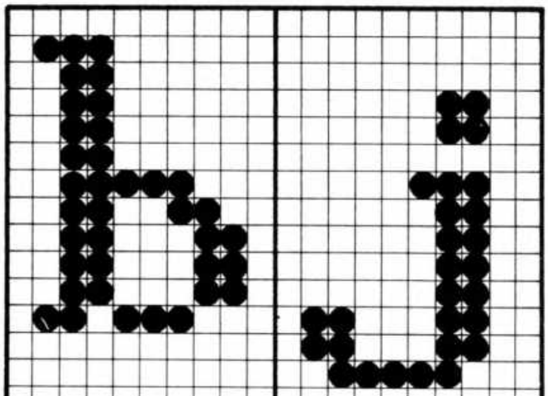

Fig. 2 *VDU pixel construction*

Our colour vision tests were the Farnsworth-Munsell 100 hue-test and the Tübinger critical flicker frequency (CFF) profile. The latter test was performed at three retinal locations (foveal and 10° to either side) to a 0·1° (approximately 6 mm) green (550 nm) then red (656 nm) target. Background luminance of 10 asb (approximately 3 cd m^{-2}) and prefilter target luminance of 1000 asb (approximately 30 cd m^{-2}) were used. The end point for each reading was taken to be the first detection of flicker when the flicker frequency was reduced from just inside perceived fusion. Plotted graphically, the usual result is a foveal peak for each colour and target size. Both these tests were performed before and within one hour of the test exposure.

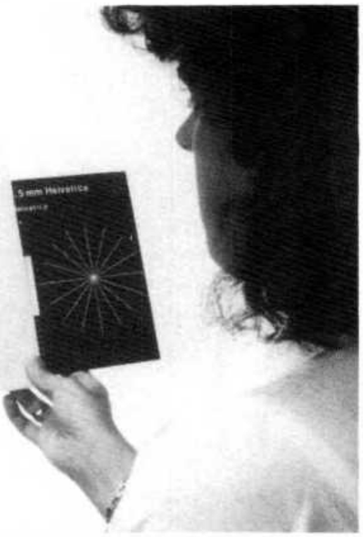

Fig. 3 *The test card in use with white card as comparison.*

Results

None of the subjects reported any visual problems with the test card prior to VDU exposure. After VDU exposure seven out of eight subjects reported no immediate after-image on the white card. The eighth subject did report an immediate after-image of a purple horizontal bar towards the lower border of the card. This faded completely within one minute.

Five subjects reported an immediate apparent change in the test card. The white lines and lettering appeared coloured. The other three subjects did not appreciate any change until the sheet of white paper was examined for comparison, when the perceived colour change became apparent. Direct questioning about colour change was not required.

The colour seen varied from pink through purple and mauve to 'blueish', but remained constant for each subject. The test card responses are summarised in Table 1. All subjects saw the white-on-black print and lines as somewhere between pink and blue. Five thought the smallest print was most coloured. Seven observed a shift towards the larger print when the test card was moved further away.

All subjects found the gratings to be coloured. Three reported that the gratings were of equal colour, three that the horizontal and two that the vertical lines were more coloured. The fan produced a similar response, but, in addition seven reported that the oblique lines were least coloured. The white box with the typewriting was seen unchanged by one subject, whereas the others saw the white box surrounded internally by a coloured fringe extending in by 1 or 2 mm. Six of these subjects saw the letters in the white box as if they had been typed on a coloured band.

On repeated testing the effect was found to decrease steadily. The first part of the test card which reverted to normal was the apparent coloured band under the type. The oblique lines on the fan followed, then the fringe round the white box. The gratings faded next, leaving the white-on-black print as the last part of the card to revert to normal.

The duration of the effect lasted from 2 to 11 hours, with an average of 5·5 hours. 100-hue testing revealed no gross change (Table 2).

Table 2 Results of Farnsworth-Munsell 100-hue testing

Subject	*Scores*	
	Before	*After*
1	50	28
2	44	12
3	12	24
4	86	38
5	12	8
6	36	53
7	35	20
8	72	83

Table 1 *Test card responses immediately after test exposure*

Subject	*Hue*	*White text*				*White box*		*Gratings*		*Fan*			*Duration hours*
		1	*3*	*5*	*CS*	*Print*	*Border*	*V*	*H*	*V*	*H*	*O*	
1 (F)	Pk	++	++	+++	Y	++	+++	++	+++	++	+++	+	6
2 (F)	B	+++	++	++	N	+	++	++	++	++	++	+	2
3 (F)	Pk	++	++	++	Y	+	++	++	+++	++	+++	+	5
4 (F)	M	++	++	+++	N	+	++	++	++	++	++	+	5
5 (M)	Pl	+++	+++	+++	N	++	+++	+++	++	+++	++	+	5
6 (M)	Pl	+++	++	++	Y	0	++	++	+++	++	++	++	3
7 (M)	Pl	++	++	+++	Y	++	+++	+++	++	++	++	+	7
8 (M)	Pl	++	++	+++	N	0	0	++	+++	++	+++	++	11

CS=colour shift towards larger letters when test car moved away. Scores indicate qualitative relative intensity of effect.
V=vertical. H=horizontal. O=oblique.
Pk=pink. B=blue. M=mauve. Pl=purple.

Table 3 *Averaged results of critical flicker frequency*

Target colour		*Degrees from fixation*		
		10 nasal	*0*	*10 temporal*
Green	before	34·0	43·5	34·5
	after	43·6	49·9	42·4
Red	before	25·2	29·0	24·7
	after	33·4	32·8	31·5

Measurement of the critical flicker frequency (CFF) profile to red and green showed a preservation of contour of the CFF profile to green, but a consistent reduction, or loss, of the foveal peak of the CFF profile to red (Table 3). This is plotted graphically in Fig. 4. The averages of the frequencies at the three retinal locations have been plotted for red and green targets before and after VDU exposure.

Discussion

We report two effects. The first was a subjective change in hue of white print and lines on a black background and to a less extent black print on a white background.

This was not a standard coloured after-image, which is gone within minutes and requires only a white background to observe.[6] One of our subjects saw a standard after-image after her test exposure. She saw a purple bar inferiorly on the white card. This was produced by the horizontal green bar at the foot of the VDU screen (the status line in the Superwriter word processing program). It was gone within one minute. A standard after-image is produced by fatiguing specific colour sensitive cones. The remaining cones respond normally, producing a relative overaction, hence the coloured after-image.

A related phenomenon occurred on viewing the test card. There were, however, important differences. This effect lasted an average of five hours after only six minutes' exposure and was not seen on plain white paper. The effect required white print on a black background or other white-black interface for its detection. This would suggest that an edge-detecting mechanism was involved.

It would seem that the green-sensitive edge detectors were fatigued. Detectors sensitive to red and blue edges were unaffected and therefore relatively overacted and produced blue-red colours at white-black interfaces. This mechanism took considerably longer to return to normal than cone fatigue and would suggest as different site of processing.

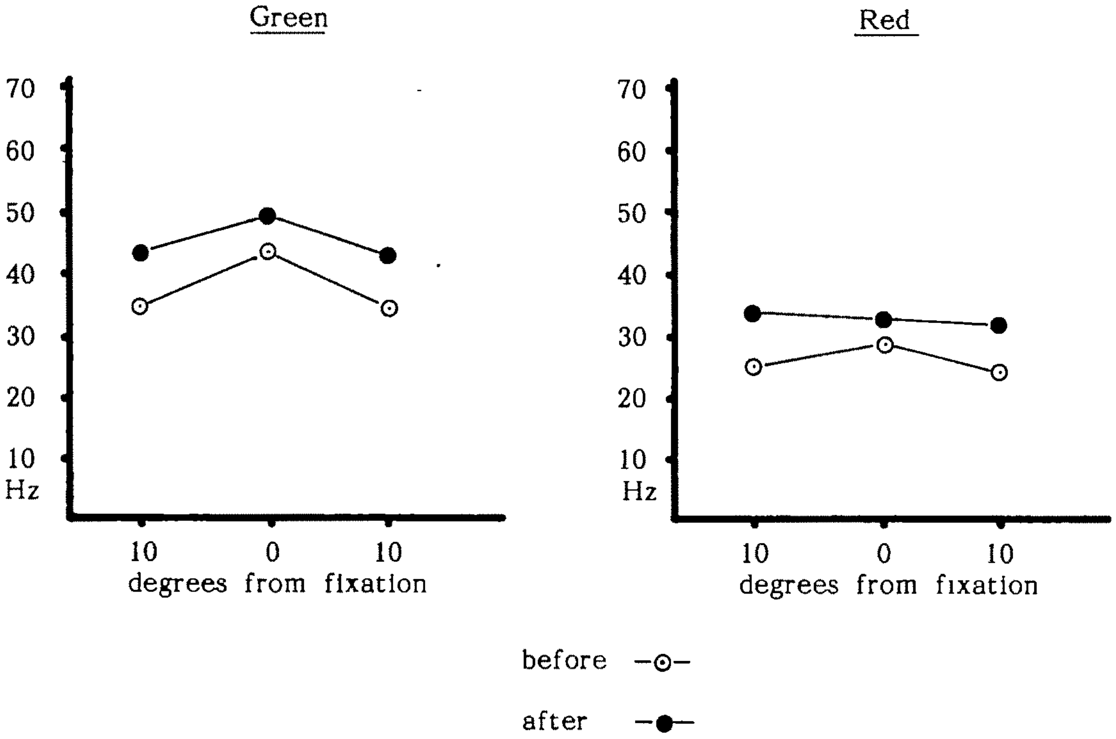

Fig. 4 *Critical flicker frequency profiles to red and green targets before and after VDU exposure.*

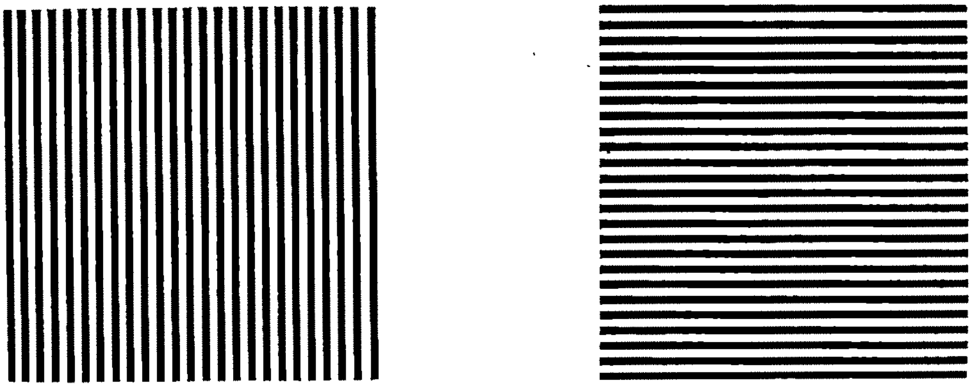

Fig. 5 *The McCollough effect test pattern.*

Fatigue of colour-coded edge-detectors had been described before[7] and is known as the McCollough effect, which is produced as follows. A horizontal and then a vertical square-wave grating is viewed alternately for several seconds. The horizontal has a blue and the vertical an orange background. After 10 minutes of this adaptation a subsequently observed test pattern (Fig. 5) looks orange on the right and blue-green on the left. The colours exchange places when the figure is rotated through 90° and is therefore orientation specific. In other words, the effect is an orientation-contingent chromatic after-effect (OCCA). Many studies have since been done on OCCAs which have increased our knowledge about them, but great debate still exists on where and how they are produced.[7–14]

We used computer generated text instead of a grating as a stimulus and believe we have fatigued *all* the green sensitive edge detectors, not just those of a particular orientation. However, given the predominance of vertical and horizontal lines in the make-up of individual letters, it is not surprising that we found the oblique lines on the fan to be least coloured. The test-card included lines much longer than any single line found in the computer text, and yet these were as coloured as the text itself. This would suggest that this mechanism of colour coded edge detection is not line-length specific.

Recent studies into OCCAs have suggested that they may represent a conditioned response.[9–13] This view was supported by the finding that, after test exposure, occluding the eyes prevented deterioration of the effect for surprising amounts of time — over 10 days in one study.[9] It was thought that presenting the test pattern weakened the conditioned response (rather like Pavlov ringing his bell without giving food) and produced decay of the effect. The effect decayed faster the more it was tested.[11] One might expect that if the subject was not tested the effect would persist indefinitely. This was found to be true only if the eyes were occluded, because incidental exposure to the white-black interfaces which exist in our everyday surroundings initiate decay of the effect.[11] Other workers have doubted the conditioning theory.[15]

One of the characteristics of OCCAs is their long duration when compared with standard after-images. The OCCA-like effect produced by the VDU has a similar longevity. In recent studies the higher the luminance of the stimulus pattern, the greater the saturation of the initial after-effect. Similarly, the longer the test pattern exposure, the longer lasting the OCCA.[16] The experienced observer can detect this effect 24 hours after an exposure of one hour (personal observation). It is possible that this after-effect is responsible for some of the subjective complaints of VDU operators, who may have this effect for prolonged periods of time. It may go unnoticed by the VDU operator for prolonged periods, as it produces only a subtle change in the observers surroundings. This may lead to visual symptoms (personal observations). With this in mind a VDU which does not produce this effect would seem preferable. The effect is not unique to the VDU, in that a colour transparency of the VDU screen with similar luminance, produces a very similar response.

We confirmed previous findings that colour vision is not affected by green-screen VDUs in that there was no significant change in the Farnsworth-Munsell 100-hue test. However, we did find a tendency towards reduction or loss of the foveal peak of the CFF profile to red. CFF is a reflection of the refractory period of the retinal neurones under study; the longer the refractory period, the lower the CFF. The expected result when the colour CFF is tested at fixation and 10° to either side is a foveal peak (except with blue light, when such a peak is difficult to detect owing to the relative scarcity of foveal blue cones). We expected there to be no change or, if the test was performed soon enough after the VDU exposure, a reduction in the foveal peak of the green CFF profile consistent with the expected changes in a standard after-image. The reason for the reduction in the foveal peak of the red CFF profile is unknown and merits further study.

We thank Mr Ivan Bradley, senior medical photographer at the Birmingham and Midland Eye Hospital, and the staff of the Department of Medical Photography, East Birmingham Hospital for the illustrations.

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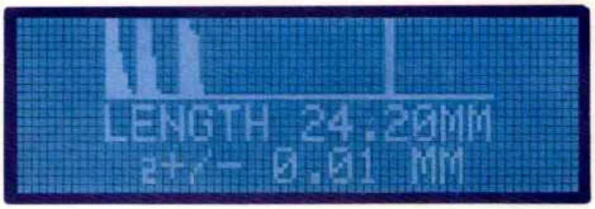

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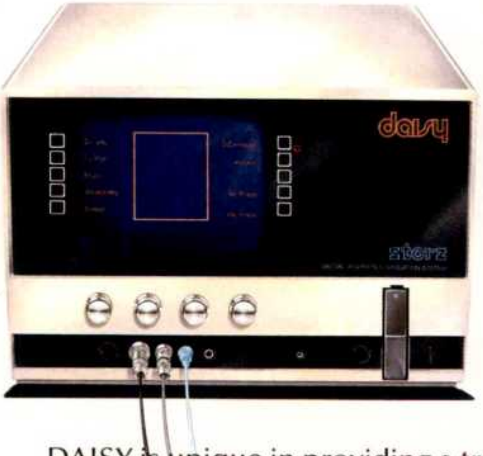

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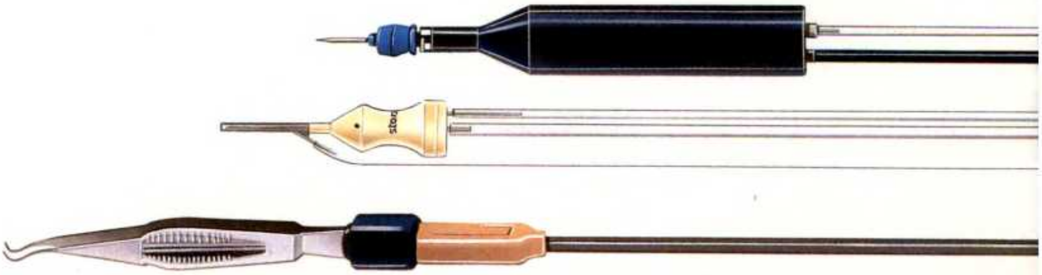

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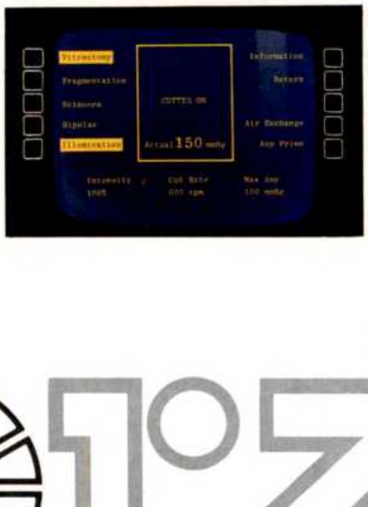

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British Journal of Ophthalmology, 1988, **72**, 829–834

Long-term follow-up of a prospective trial of argon laser photocoagulation in the treatment of central serous retinopathy

LINDA FICKER, GILLIAN VAFIDIS, ADRIAN WHILE, AND PETER LEAVER

From Moorfields Eye Hospital, City Road, London

SUMMARY In a prospective randomised trial of argon laser photocoagulation in the management of central serous retinopathy, long-term follow-up (6·4 to 12·1 years) revealed no evidence that treatment significantly influenced the visual outcome as measured by the Snellen chart and by the Farnsworth-Munsell 100-hue test. Treatment did not reduce either the recurrence rate or the prevalence of chronic disease. Complications of treatment were uncommon. The justification for argon laser photocoagulation appears to be limited to the hastening of symptomatic relief by earlier resolution of serous detachment.

In central serous retinopathy (CSR)[1] there is serous detachment of the macular retina. It generally follows an acute course, with spontaneous resolution and good recovery of visual function. A chronic course supervenes in a minority of patients, in whom progressive retinal pigment epithelial changes are associated with permanent impairment of visual function. This course may be a consequence of either multiple recurrent attacks or chronic detachment.

The development of suitable photocoagulation techniques[2] has enabled accurate treatment to the source of subretinal fluid as determined by fluorescein angiography.[3,4] Acute studies have shown that the duration of macular detachment is reduced by focal application of argon laser photocoagulation to the sites of 'leakage' in the retinal pigment epithelium.[5-8] Resolution of serous detachment is associated with symptomatic improvement following photocoagulation,[7,9-11] though it is acknowledged that symptoms may persist to a variable degree despite reattachment of the retina.[4,12]

Sixty-seven eyes in a randomised controlled clinical trial, were initially reported on in 1979.[5] In the original study there was no significant difference in final visual outcome between the treated and untreated groups of patients as judged by Snellen acuities and Farnsworth-Munsell 100-hue discrimination. No patient suffered visual loss because treatment was withheld. The purpose of our long-term study was to establish the recurrence rate of CSR in treated and untreated patients. In addition we wished to identify any differences in long-term visual outcome between the two groups and any complications of treatment, factors which are important in a recurrent disease affecting the socioeconomic potential of young people.

Patients and methods

Seventy consecutive eyes with CSR in 69 patients referred to the Retinal Diagnostic Department of Moorfields Eye Hospital between 1973 and 1977 satisfied the following criteria for admission to the study: (1) corrected visual acuity (VA) of 6/12 or better; (2) retina detached at the fovea; (3) retinal pigment epithelial (RPE) defects smaller than one disc diameter (DD); (4) no symptomatic improvement since the onset of the attack; (5) absence of subretinal exudates; (6) no cystic retinal oedema present; (7) no associated ocular disease; (8) informed consent to participate in the study. Patients were selected at random by drawing a card in a sealed envelope so that half were treated and half untreated. It was ruled that eyes in the untreated group in which the corrected VA fell to less than 6/12 during the study or which developed cystic retinal oedema or subretinal exudates should be treated and classified as cases of failed conservative management. No patient was withdrawn from the study for these reasons.

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Fluorescein angiography was used to identify the leaking site, which was then treated with the Coherent Radiation 800 argon laser using burns of 50 to 200 µm in diameter, 20 to 200 milliseconds in duration, and 150 to 400 milliwatts of power. Initial and final examinations included clinical history, assessment of best corrected VA, Farnsworth-Munsell 100-hue error score, funduscopy by both the Hruby lens and the indirect ophthalmoscope, and fluorescein angiography.

Of the 70 eyes entered into the study three were excluded from the original report because they had not been followed up for six months. A further four had missed visits. Hence data from 63 eyes were initially reported. Of the 70 eyes 44 (63%) were available for review at intervals ranging from 6·4 to 12·1 years after their initial presentation. Changes in patients' domicile and social status made contact difficult, while some patients, particularly those who had not received treatment, were reluctant to spend time attending for review. Twenty-one patients could not be traced, two had died, two refused to attend, and one was known to have emigrated.

The mean follow-up for the untreated group (n=19) was 9·5 years and for the treated group (n=25) 9·1 years. In the untreated group six patients were treated for recurrence after the initial attack and were reclassified as a separate group of subsequently treated patients (group S). The remaining 13 untreated patients were designated group U and the 25 treated patients group T.

Results

Persistent symptoms (mostly paracentral scotomata, minimal distortion, and colour desaturation) were reported by 23 patients; 6 (47%) in group U, 5 (83%) in group S, and 12 (48%) in group T. Visual acuities among these patients were 6/9 or better, with the exception of one patient with extensive disease whose VA fell to 6/60 in group S (Fig. 1). The scores for visual acuity and 100-hue discrimination for this patient were excluded to allow statistical analysis.

VISUAL ACUITIES

Visual acuities were converted to a simple numerical scale from 1 (6/4) to 5 (6/12). The mean VA on presentation, as originally reported, was 3·9 in the control group (3·8 in group U and 4·2 in group S) and 3·7 in the treatment group. At final follow-up the visual acuities for the three groups were 2·0 (group U), 2·0 (group S, excluding the only patient in the study to fall below 6/12 to 6/60), and 1·9 (group T). Visual acuities of 6/6 or better were achieved in 37 patients of the 44 at long-term follow-up; 12 (92%) in group U, 5 (83%) in group S, and 20 (80%) in group T. There were no significant differences in VA between untreated patients (group U) and patients randomised to treatment (group T), either initially (p=0·606) or at final follow-up (p=0·489) (Mann-Whitney U test).

HUE DISCRIMINATION

Results were available for 35 cases. The mean error scores at presentation were 243 in group U, 284 in group S, and 290 in group T. The final error scores were 104 in group U, 99 in group S (excluding the patient with final VA 6/60 whose score was 787), and 112 in group T. These represent changes of 59%, 70%, and 60% respectively. There were no statistically significant differences between the error scores for untreated patients and those randomised to treatment either initially (p=0·67) or at final follow-up (p=0·94).

RECURRENCES

Thirteen patients gave histories of recurrence during the follow-up period—37% of the original control group and 28% of the treatment group. The difference was not statistically significant (p=0·76). A further eight were found to have fluorescein angiographic appearances consistent with recurrent disease. Hence angiographically documented recurrence occurred in 53% of the original control group and 44% of the treatment group. This difference was not significant (p=0·79).

Of the 13 symptomatic patients five presented at the time of their recurrence. The site of recurrence could therefore be identified in these cases. Two patients (group U) presented within 12 months of the original episode and three presented later, between 15 and 29 months (two treated patients and one control). The recurrences were multifocal and included the original focus of leakage (Fig. 2) in the untreated patients. Recurrence occurred within 200 µm of the original leak, on the border of treated pigment epithelium, in treated patients. One treated patient had a new remote site of leakage in addition to two new leaks adjacent to the original foci (Fig. 3).

The chronic phase of the disease represents a threat of permanent visual loss and is characterised by progressive retinal pigment epithelial disturbance. Of the 41 patients on whom follow-up fluorescein angiography was performed two untreated, five treated patients, and two from group S were found to have diffuse hyperfluorescence exceeding 3000 µm (2 DD). Of these, eight gave no history of recurrence during the period of progressive retinal pigment epithelial change. The distribution of this change was inferior to the original sites of documented leakage in each case. There was no difference in the prevalence of chronic disease between the groups.

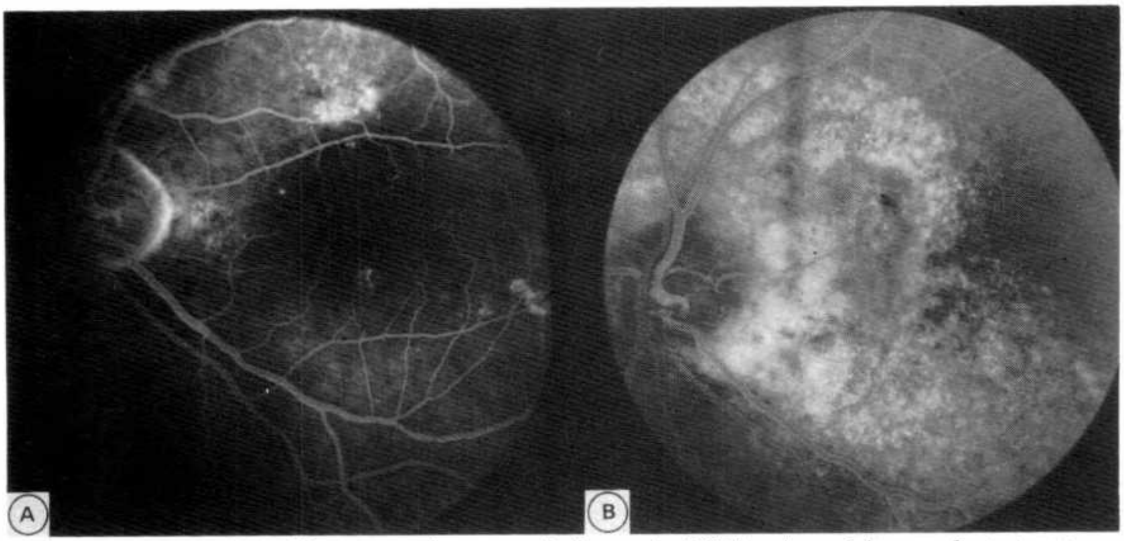

Fig. 1 A: *Resolution of CSR following treated recurrence.* B: *Progressive RPE disturbance eight years after treatment.*

COMPLICATIONS OF TREATMENT

Choroidal neovascularisation was identified at the sites of treated focal leakage in two patients, but neither was symptomatic (Fig. 4). In both cases the treatment site was within 750 µm of the fovea. A further patient showed angiographic evidence of leakage without a clearly identifiable capillary tuft at the photocoagulation site; choroidal neovascularisation could not be excluded as the cause. The neovascular membranes did not involve the fovea at follow-up intervals between eight and nine years after treatment, and VAs in these three eyes were 6/5 or better.

Discussion

The main issue we are concerned to address is the role of photocoagulation in the management of central serous retinopathy. We defined our diagnostic criteria and selected patients with good initial visual acuity for whom a decision concerning treatment presents a dilemma given the expected spontaneous resolution of the disease.

The long-term visual outcome in our study was good and was not significantly different in treated patients as compared with untreated patients. A similar result was observed in a randomised trial of

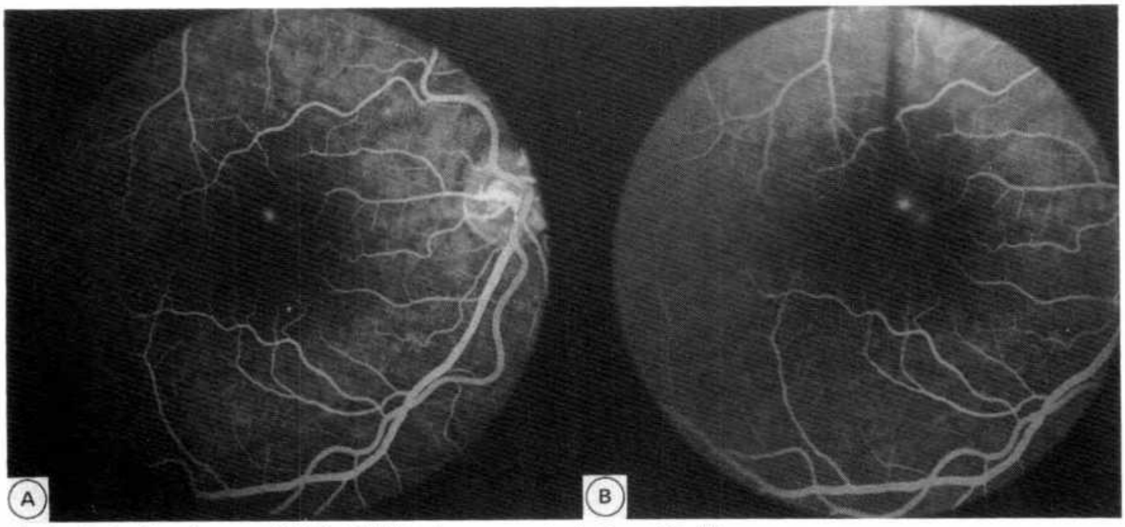

Fig. 2 A: *Leakage in acute CSR.* B: *Multifocal recurrence including original focus.*

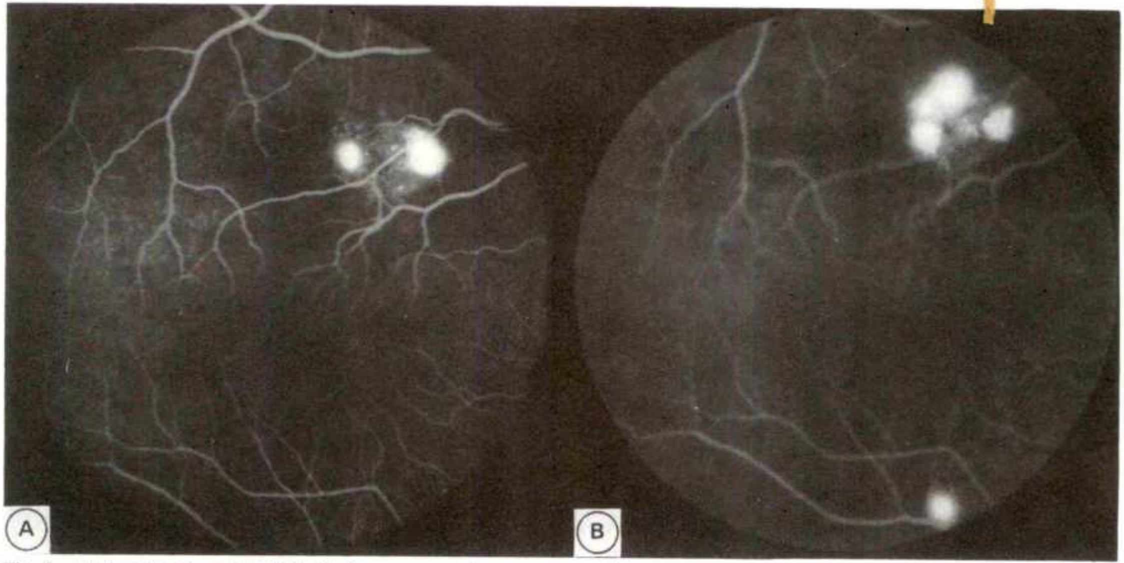

Fig. 3 A: *Leakage in acute CSR.* B: *Recurrence adjacent to treated sites.*

treatment by Watzke *et al.*,[7] while Klein *et al.*[13] reported spontaneous recovery with vision of 6/12 in 27 consecutive patients treated conservatively.

The rationale for treatment as postulated by Maumenee[3] was that central serous retinopathy resulted from leaks through defects in Bruch's membrane and the adjacent retinal pigment epithelium and that focal photocoagulation would occlude these defects.

While it is true that direct photocoagulation reduces the duration of detachment in comparison with indirect or no treatment,[8 14] the mechanism by which this is achieved remains controversial. Spitznas[15] has reviewed the experimental evidence on the nature of the retinal pigment epithelial abnormality. He postulated a reversal in the direction of water transport across the abnormal retinal pigment epithelium such that this occurs from the choroid towards the neuroretina.[16] Photocoagulation may achieve resolution of detachment by destroying the abnormal focus of pigment epithelial cells and inducing migration of adjacent epithelial cells across the treatment site, hence restoring function to the focus of 'leakage'. In our study recurrence did not occur at

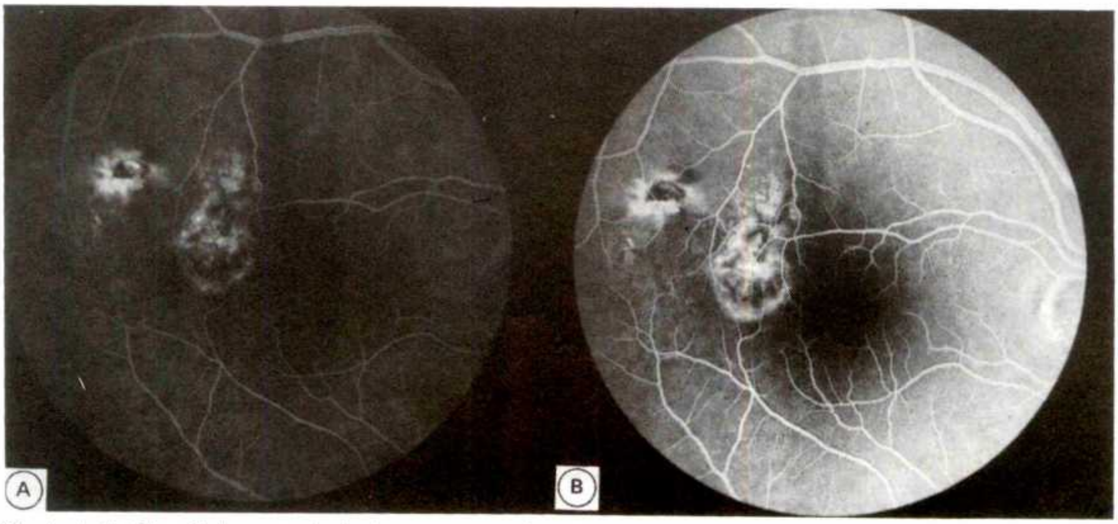

Fig. 4 A, B: *Choroidal neovascularisation at treatment site.*

the treatment site but from a focus about 200 μm from it, while recurrence in untreated patients did indeed occur at the site of the original leak. There was, however, no difference in the recurrence rate of acute CSR between the two groups.

The recurrence rate among treated and untreated patients has not hitherto been established for a prospective, randomised trial, and existing data are not concordant. No significant difference was found by Watzke *et al.*[14] in a prospective study, nor by Nanjiani[11] or Gilbert *et al.*[17] in retrospective studies, while Dellaporta[18] and Robertson and Ilstrup[8] believed there was a reduced incidence of recurrence among treated patients. Robertson and Ilstrup[8] found no recurrence among a small number (n=7) of treated patients whose outcome was reported at 18-month follow-up. In our long-term prospective study we found no evidence that treatment reduced the recurrence rate of acute CSR.

Of particular interest was the finding that treatment did not reduce the incidence of chronic disease. The concept of chronic disease is now widely accepted, though it is uncertain whether this represents recurrence or the chronic passage of fluid across the retinal pigment epithelium (RPE) towards the neuroretina.[7,18–21] The manifestation of chronic disease is the involvement of large areas of abnormal RPE, contiguous with the original site of leakage and often gravity-dependent, which are angiographically evident as areas of hyperfluorescence at the level of the RPE. Our results do not support the concept that chronic disease results from recurrence, since only one patient with chronic disease had a history of recurrent disease and of the 13 with symptoms of recurrent attacks only one had chronic disease.

The most serious complication of treatment is choroidal (subretinal) neovascularisation as reported by Schatz *et al.*[22] It is assumed that, when a diagnosis of CSR is made, early neovascular membranes (NVM) can be specifically excluded as a cause of serous detachment. In earlier series this possibility was not fully appreciated, and of the 27 cases reviewed by Schatz *et al.* a proportion did indeed have NVMs rather than CSR at the time of diagnosis. In others NVMs were suspected but not proved. Of the cases of true CSR in which development of an NVM followed laser treatment, the common factor was the proximity of the leakage site to the fovea. Schatz *et al.* postulated that the combination of high-power densities delivered and the high concentration of absorbent pigments at the fovea probably resulted in ruptures of Bruch's membrane, hence stimulating neovascularisation. These cases were symptomatic and therefore presented to an ophthalmologist. NVMs have not been reported in many series. Watzke *et al.*[14] reported two among 20 treated cases and these involved central vision. Our cases, however, demonstrate that NVMs distant from central vision may be both asymptomatic and stable, which may account for the paucity of NVMs complicating treatment which have been reported, particularly in retrospective studies.

Most patients with CSR who present with VAs equal to or better than 6/12 achieve recovery of good visual acuity, which is hastened by laser treatment. The only patient to suffer visual deterioration was originally in the untreated group. The visual outcome, however, as measured by Snellen acuities and Farnsworth Munsell 100-hue discrimination, does not necessarily measure all attributes of visual function and permanent symptoms existed in patients with good recovery of function as measured by these techniques. It was found by Chuang *et al.*[23] that rod threshold elevation during acute CSR exceeded 3·5 log units and was directly related to the height of the detached retina. Recovery of threshold to within 0·5 log unit of normal was recorded within three weeks of clinical resolution. Thus a small long-term deficit remained. Chronic disease was characterised by threshold elevation of 3·5 log units in areas of abnormal RPE in the absence of detectable neurosensory detachment.

There was incomplete ascertainment, since only 63% of the patients entered into the trial were reviewed, and it is possible the results may be biased. This is unlikely, because the main reason for failure at follow-up was that patients were untraceable, and this would not be expected to be biased by visual outcome.

We conclude that treatment does not reduce the incidence of recurrent disease or of chronic CSR in which progressive retinal pigment epithelial disturbance presents a real threat of permanent visual loss. Our results suggest that the conclusions drawn from the original study remain valid; that the role of argon laser photocoagulation in CSR with good visual acuity is limited to hastening relief of symptoms by achieving speedier resolution of serous detachment.

We thank Professor Alan Bird for his help and encouragement in the preparation of this manuscript, Peter Clark for the statistical evaluation of our data and the Department of Medical Illustration, Moorfields Eye Hospital, for preparation of the photographs. The study was supported by the Locally Organised Research Scheme, Moorfields Eye Hospital.

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Changing fluorescein angiographic appearance of a subretinal membrane

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SUMMARY A patient is described in whom a post-traumatic subretinal membrane changed with time from a hypofluorescent to a hyperfluorescent appearance. It is suggested that the early hypofluorescence was due to a masking effect of the hyperplastic retinal pigment epithelium and the late hyperfluorescence to pigment defect and staining of the membrane.

Subretinal fibrosis is a clinical entity infrequently reported. It may be secondary to trauma,[1] retinal detachment,[2] or uveitis.[3] The fluorescein angiographic features of the subretinal fibrosis are controversial, since it has been described as a lesion showing staining[3] or lacking any fluorescence.[1]

We followed up a case of post-traumatic subretinal fibrosis for some years and record previously unreported changes in the fluorescein angiographic characteristics of the lesion.

Case report

A 47-year-old man, hit in the right eye with a thick rubber band, was observed three months after the injury. The retina showed a macular cyst and, superotemporally to the macula, a greyish, star shaped area of subretinal fibrosis (Fig. 1, left). The fluorescein angiography in the early phase showed masking hypofluorescence of the fibrotic tissue, except for the vertices of the lesion, which displayed transmitted hyperfluorescence (Fig. 1, centre). The hyperfluorescence increased in the late venous phase, but the lesion did not show leakage (Fig. 1, right). The visual acuity was 20/60.

After three years the macula developed two holes. The star-like lesion did not change its shape, though it acquired a whitish colour (Fig. 2, left). Early in fluorescein angiography the area of fibrosis showed transmitted hyperfluorescence (Fig. 2, centre), and later the hyperfluorescence increased owing to staining (Fig. 2, right). The visual acuity was 20/30, and fixation occurred along the temporal edge of the larger macular hole.

Discussion

After retinal damage the cells of the retinal pigment epithelium may proliferate in the subretinal space,

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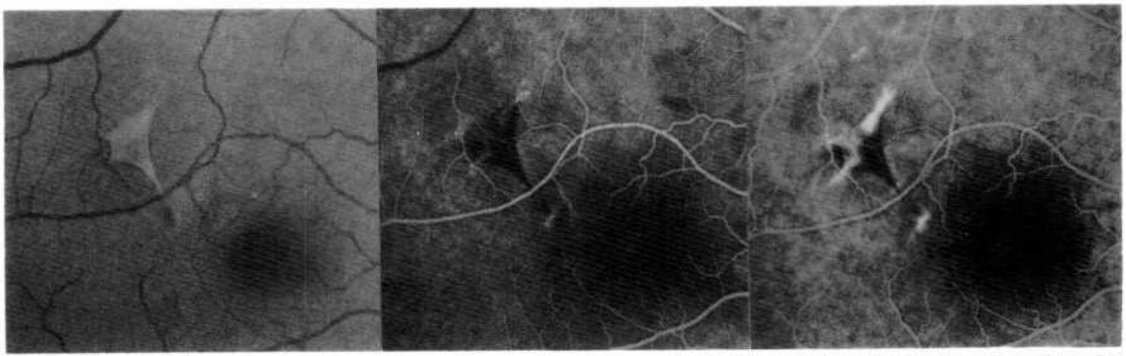

Fig. 1 *The retina shows a greyish subretinal membrane and a macular cyst (left). The membrane is hypofluorescent from the early phase of fluorescein angiography (centre), but the vertices of the lesion display increasing hyperfluorescence (right).*

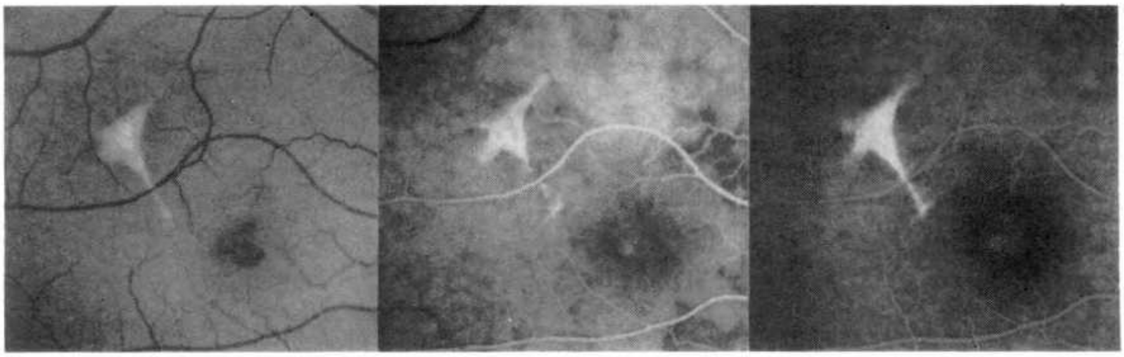

Fig. 2 *After three years the subretinal membrane acquired a whitish colour and the macula developed two holes (left). The fluorescein angiography shows transmitted hyperfluorescence of the whole lesion (centre) and late staining of the membrane (right).*

producing connective membranes.[4] At times these pigment epithelium cells may flatten, lose their pigment granules, and degenerate, so that the main component of the membrane will be the connective tissue.[5]

In the case reported here the grey subretinal membrane appeared hypofluorescent, probably because it was mainly composed of retinal pigment epithelium cells that masked the choroidal fluorescence. The vertices of the membrane, which are its oldest parts, had lost the cellular component and showed transmitted hyperfluorescence and staining. After some years, when the membrane acquired a whitish colour and was probably formed mainly of fibrous tissue, it showed hyperfluorescence from the early phases of fluorescein angiography. It can be supposed that the degeneration of the retinal pigment epithelium located under the membrane caused the early transmitted hyperfluorescence, and the staining of the connective membrane caused the late hyperfluorescence.

Thus it seems that the fluorescein angiographic appearance of the subretinal membranes can give information about the age of such membranes.

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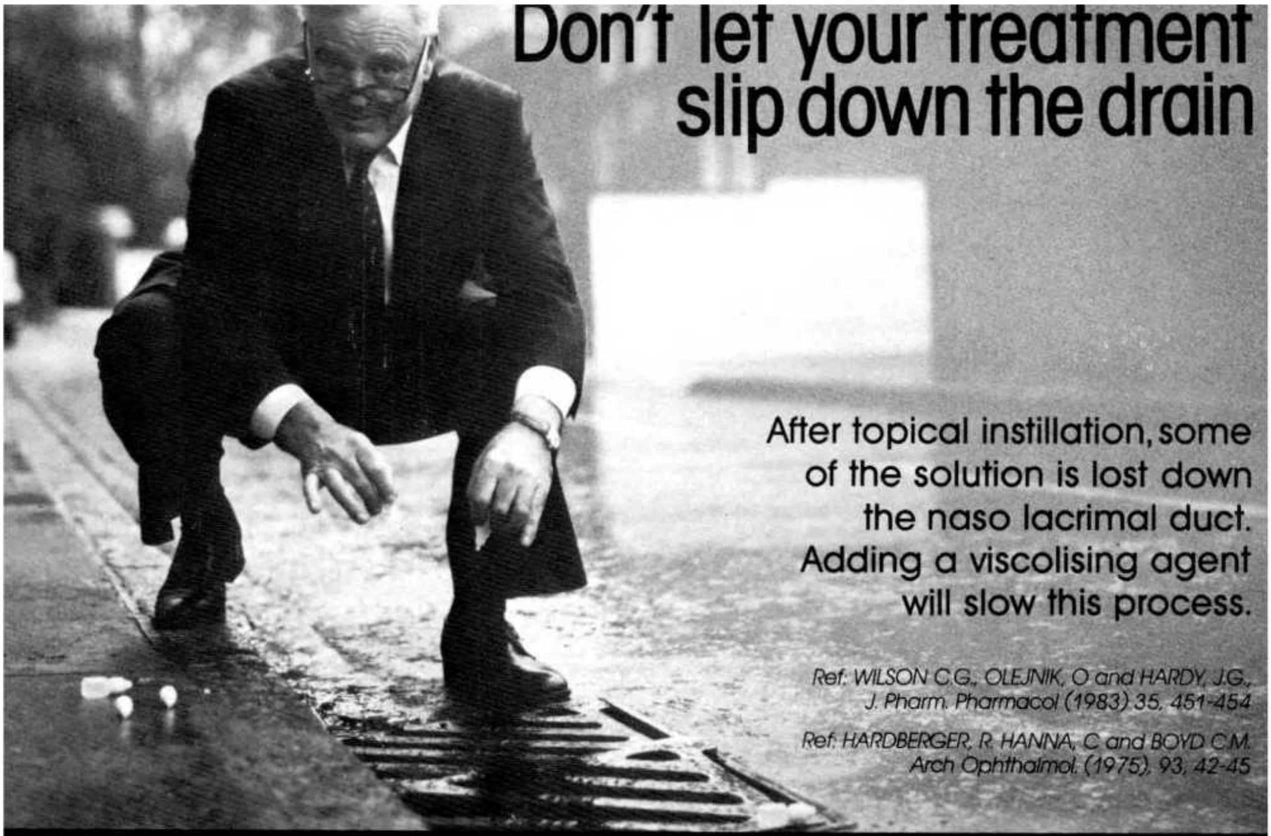

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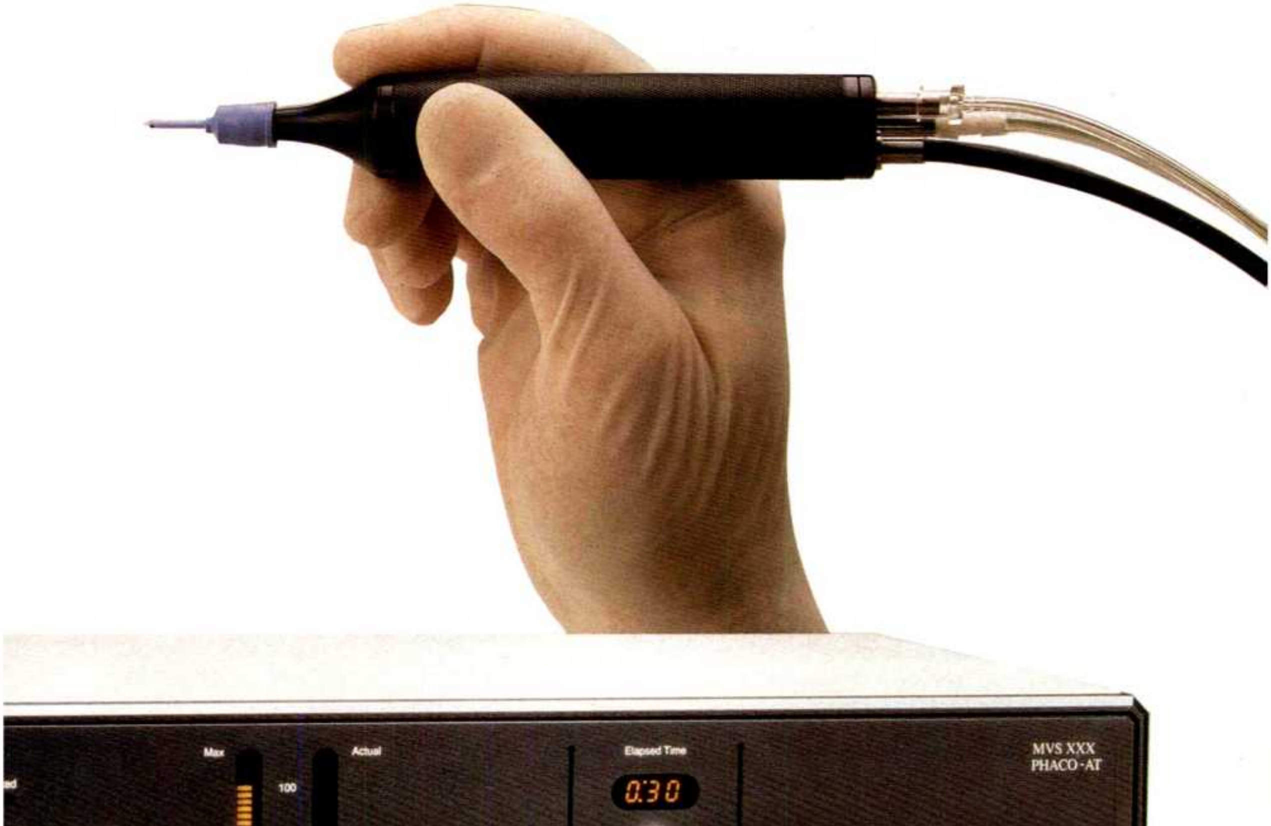

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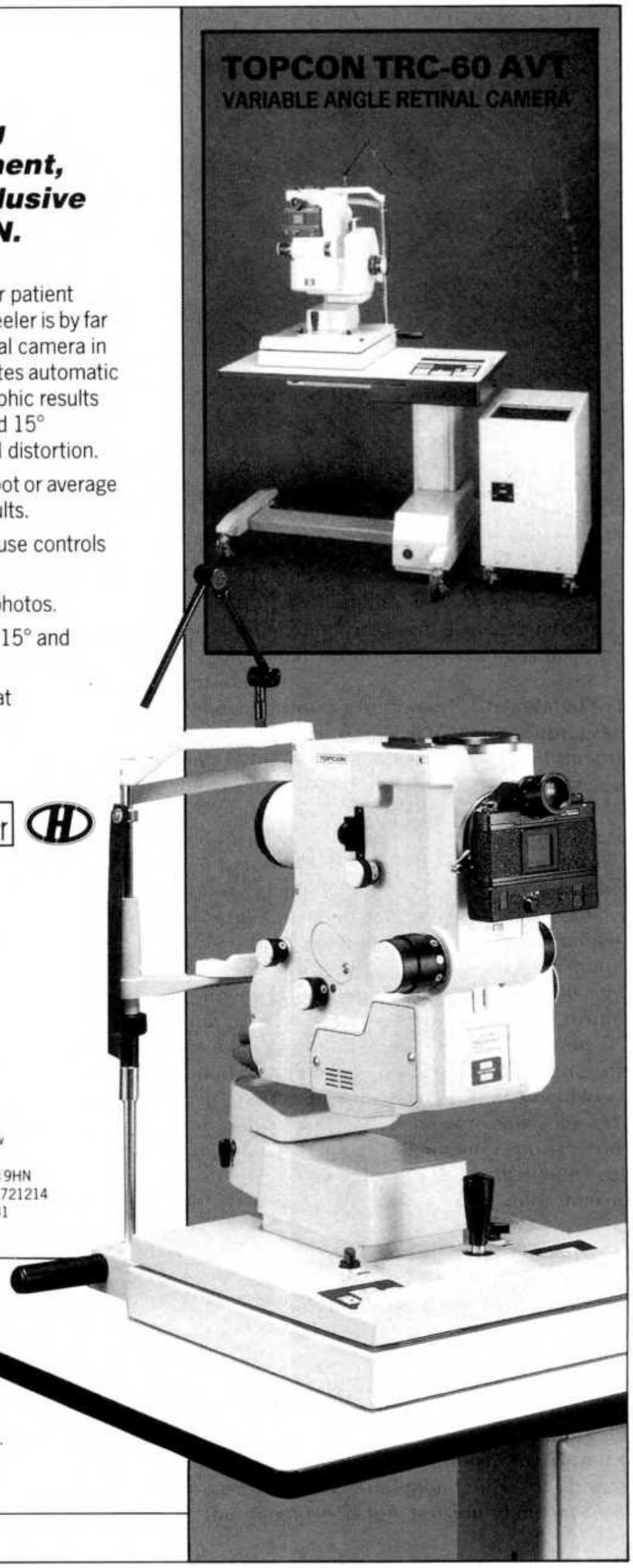

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British Journal of Ophthalmology, 1988, **72**, 837–840

Photocoagulation of raised new vessels by long-duration low-energy argon laser photocoagulation – a preliminary study

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SUMMARY Direct laser treatment of retinal neovascularisation is indicated when regression has not been brought about by retinal photocoagulation. Current treatment regimens involve multiple laser applications to the neovascular complex. Long-duration low-energy burns have the advantage of slowly heating the tissue without engendering disruption. We report the use of this treatment as a means of occluding the feeder vessels to a neovascular network. The application of argon blue-green laser treatment at 0·1 watt for 60 seconds at two adjacent points on a feeder vessel was found to give rise to permanent vascular occlusion without causing complications.

One of the primary intentions of the development of photocoagulation was to occlude raised retinal new vessels. However, even with the argon laser, with its coherence, selective absorption, and ease of variation of the size and duration of each burn, direct treatment was often found to be ineffective and difficult.[1] It was subsequently found that the surrounding retinal damage engendered by the photocoagulation treatment appeared to bring about regression of such aberrant vasculature as a secondary phenomenon. Panphotocoagulation was thus introduced as a means of inducing regression.[2-4] Nevertheless, raised new vessels continue to present problems when panphotocoagulation fails to induce regression.[5] Argon laser treatment strategies have thus been devised in which multiple lesions are applied repeatedly to the neovascular network in order to induce regression. Such treatment is time consuming and may be complicated by vitreous haemorrhage,[5 6] retinal holes, and preretinal fibrosis.[1]

Recently long-duration (10–30 seconds) low energy (0·2–0·4 watt) laser photocoagulation has been advocated as a means of treating choroidal melanoma.[7 8] However, to our knowledge similiar treatment has not hitherto been described as being applied to raised new vessels.

We report on a patient with perivasculitis retinae (Eales' disease) in whom repeated photocoagulation of ischaemic retina failed to induce regression of neovascularisation, but for whom the direct application of long-duration low-energy treatment was found to be effective in producing closure of the aberrant vasculature.

Patient and methods

A 29-year-old healthy male presented with sudden loss of vision in the left eye. Clinical examination revealed a vitreous haemorrhage arising from abnormal raised new vessels in the inferonasal quadrant of the left peripheral retina. The aberrant vasculature comprised feeder vessels from the venous side and a fine network of minute vessels and gliosis underlying a detached posterior vitreous face (Fig. 1). Fluorescein angiography showed patent abnormal vessels arising from the venous circulation, which was surrounded by areas of capillary closure (Fig. 2). This late frame showed leakage from the neovascular complex. Unfortunately the patient was violently sick following intravenous fluorescein, and no further fluorescein angiography was performed. Blue-green argon laser photocoagulation was carried out over the area of capillary closure. No direct treatment was administered to the abnormal vasculature at this stage. No regression of the new vessels was engendered by this treatment, and further coagulation of the ischaemic area was performed six weeks later. The patient was followed up for six months but again there was no evidence of regression (Fig. 3).

In view of the risk of recurrent vitreous haemorr-

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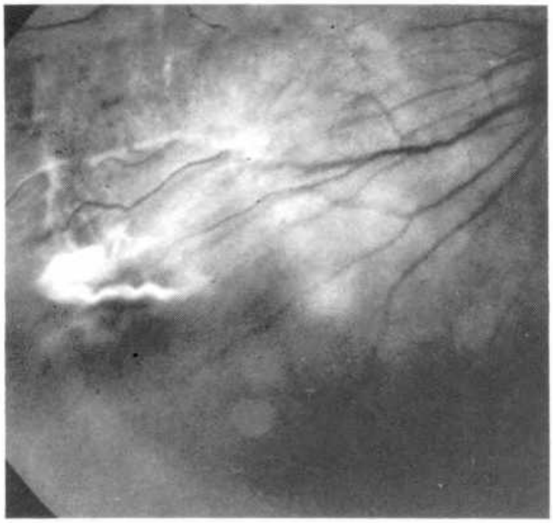

Fig. 1 *Fundus photograph of neovascular membrane overlying the left inferonasal retina.*

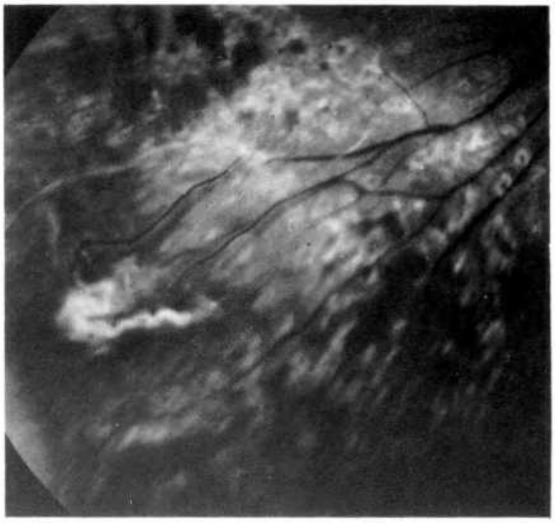

Fig. 3 *Fundus photograph taken after two sessions of argon laser photocoagulation of the ischaemic retina. There has been no regression of the neovascular membrane.*

hage direct photocoagulation of the abnormal new vessels was carried out. There were two main feeder vessels which each divided into two main branches; three of these main branches were elevated from the retina. Treatment was applies as follows. Topical local anaesthetic was instilled and a three-mirror contact lens applied. The biophysic medical argon-krypton laser was employed with the time setting adjusted to continuous. The argon blue-green laser was aimed at a point on the abnormal vessel and the foot switch depressed. Two adjacent points along the uppermost vessel were treated with 0·15 watt, with a 50 μm spot size, delivered continuously for 30 seconds. The duration of laser application was timed to the nearest second. (The laser employed has a protective filter between the patient and the operator, and thus the position of the treatment being applied can be visualised throughout.) After

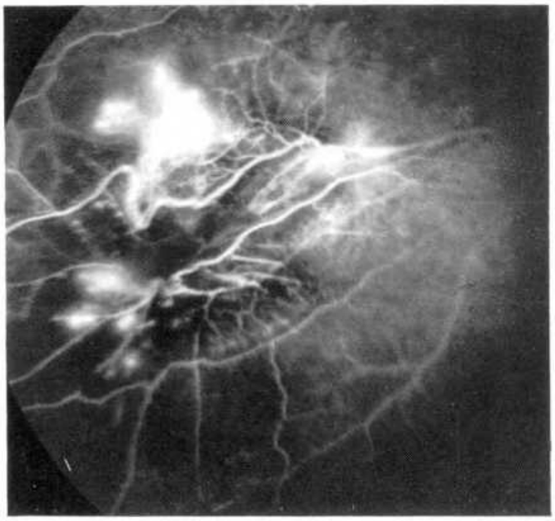

Fig. 2 *Fluorescein angiogram taken at 52 seconds showing peripheral retinal capillary closure and leakage of dye from raised new vessels.*

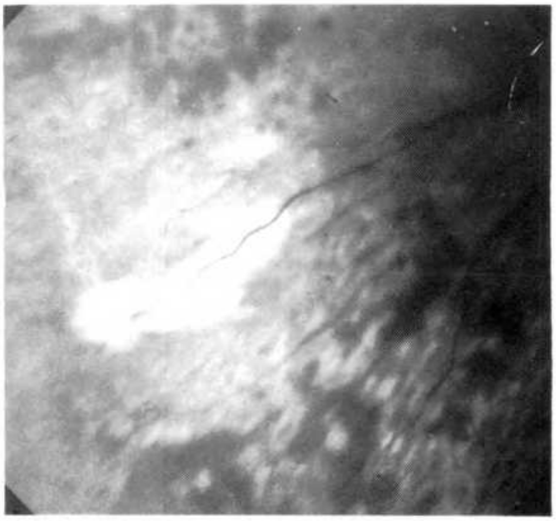

Fig. 4 *Fundus photograph taken 48 hours after long-duration low-energy argon blue-green laser photocoagulation of the upper feeder vessel supplying the neovascular membrane.*

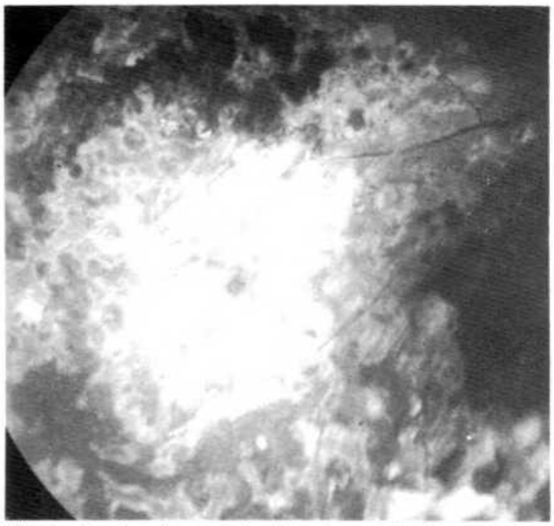

Fig. 5 *Fundus photograph taken six months after long-duration low-energy argon blue-green laser photocoagulation of the three feeder vessels supplying the neovascular membrane. Complete regression of the new vessels has taken place.*

this first application the treated vessel was occluded by the following day, but a flame shaped haemorrhage was later observed adjacent to the vessel (Fig. 4).

Consequently for further applications a lower energy setting was used (0·1 watt) with twice the duration of exposure (60 seconds). The two remaining raised vessels were treated by the same method at the same sitting. On this occasion narrowing of both vessels was seen the next day, and closure was observed four days later. Six months after treatment the new vessels remained closed (Fig. 5).

Discussion

Elevated new vessels and vascular loops have hitherto proved difficult to occlude by direct photocoagulation. The light emitted by the argon blue-green laser is absorbed by haemoglobin.[9] It thus provides an appropriate means of occluding new vessels. Treatment strategies at present employed involve the application of repeated, multiple, relatively high-energy low-duration burns to the abnormal vessels. Such vessels are friable and susceptible to rupture, particularly if laser treatment is too heavy. It is thus not surprising that this time consuming mode of treatment is commonly accompanied by haemorrhage, the very complication which the treatment is designed to avoid.

The rate of blood flow in the main retinal vein is between 12 and 14 mm per second as determined by the differential laser Doppler method.[10] Thus, when laser energy is applied to the retinal vein, heat it dispersed by a flowing blood column. For this reason treatment strategies have been designed which begin by occluding the terminal portions of the neovascular fronds in which the rate of blood flow is lower. The rationale of the treatment described in the present study was gradually to heat the venous feeder vessel and thereby induce stasis and thrombosis of the blood column between two points of coagulation. Vessel closure is brought about without vitreous haemorrhage in a single short treatment session.

Experimental work with rabbits has shown moderate swelling of the nerve fibre layer after light coagulation, and it is possible that this phenomenon may contribute to the vessel closure.[11] Vascular spasm may also be a factor in giving rise to narrowing of the vein.[12] Once the laser treatment has brough about stasis within the vessel being treated, it is likely that the heat being taken up by the blood column would be transmitted to the adjacent vessel wall. In addition, the oxyhaemoglobin will become reduced to haemoglobin in a static blood column. Reduced haemoglobin has a higher energy absorption for argon blue-green laser than oxyhaemoglobin,[13] thus potentiating the effect of treatment.

Only lasers in which a protective filter rather than a shutter is fitted can be used for the type of treatment described in this paper. The filter precludes accurate assessment of the visible effect of the retinal burn. The area of whitening is seen only when the laser is switched off. Moreover 'closure' of the vessel being treated is not observed during treatment but is seen shortly afterwards. Thus the time duration of treatment must be empirical and awaits definitive histopathological investigation.

As the time duration of laser application is reduced and the energy level increased, the focal temperature becomes higher. This can cause vaporisation and haemorrhage in the target tissue.[14] Photocoagulation regimens which include initial treatment of the feeder vessel to cause spasm have been described.[15] However, we suggest that by increasing the time and concomitantly reducing the energy the safety margin for treating retinal new vessels is increased. Furthermore, direct closure of retinal new vessels by using multiple laser applications is time consuming for the clinician and is uncomfortable for the patient. On the basis of our experience with this patient we would suggest that any studies designed to delineate the optimum energy and time criteria for vessel closure could begin with the findings we have described.

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Evaluation of a non-mydriatic camera in Indian and European diabetic patients

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SUMMARY The value of the Canon CR3-45NM non-mydriatic fundus camera in screening for diabetic retinopathy has been assessed in two ethnic groups, namely, 45 Indian and 40 European diabetic patients. There was 72% agreement between ophthalmoscopy by an ophthalmologist and the photographic assessment, and 100% agreement on clinically important lesions requiring treatment. However, peripheral retinal lesions, seen on ophthalmoscopy but lying outside the photographic field, occurred in 4% of eyes. 6% of photographs were totally unassessable and an additional 12% were only partially assessable. The prevalence and severity of retinopathy was similar in Indian and European patients. The advantages and disadvantages of the non-mydriatic camera in screening for diabetic retinopathy are discussed.

Ophthalmoscopy and conventional retinal photography are the two methods most often used to diagnose diabetic retinopathy. Both require pupillary dilatation, which may be a disadvantage in epidemiological studies and in busy clinic settings, when many patients need to be screened relatively quickly. The recently introduced non-mydriatic fundus camera[1,2] seems to be the ideal tool for these situations, but its evaluation is incomplete. The present study was undertaken to assess the value of the Canon CR3-45NM camera in screening for retinopathy in a busy diabetic clinic. We particularly wished to see whether the camera was suited for use in Indian 'Asian' patients who have dark irises, which may dilate less readily, and have pigmented fundi, which might be more difficult to evaluate.

Material and methods

PATIENTS

Forty-five Indian patients (33 male, 12 female) and 40 European patients (23 male, 17 female) were studied. They were consecutive patients attending the Ealing Hospital diabetic clinic who met the entry criteria, which were an age at diagnosis greater than 20 years, a known duration of diabetes of at least four years, and no history of ketosis. Fifteen Indian and 24 European patients were receiving insulin treatment. Other clinical features are shown in Table 1.

METHODS

Visual acuities were assessed in a darkened room at 6 m by means of a standard Snellen chart with internal illumination. The best visual acuity obtained with the patient's own glasses and/or pinhole was recorded. The patient was then seated in a dark room for not less than five minutes, until adequate dilatation of the pupils, checked with the camera, had been achieved. Photography was performed with the Canon CR3-45NM non-mydriatic wide-angle (45°) camera, used in a totally darkened room. The camera uses an infrared illumination source instead of the common white light. The fundus is viewed prior to flash

Table 1 *Clinical features of Indian and European patients*

	Indians (45)	*Europeans (40)*	*p*
Mean age (years)	54·9	62·1	<0·01
Median known duration (years)	8	12	NS
Mean fasting blood glucose (mmol/l)	10·8	12·1	NS
Mean body mass index*	26·2	25·8	NS
Hypertension†	10	13	NS

*Body mass index = weight (kg)/height (m)^2.
†Hypertension diagnosed by WHO criteria.

Correspondence to Dr E M Kohner.

exposure by means of an infrared-sensitive video camera built into the fundus camera, and is displayed to the operator on a small TV monitor. No direct view through the fundus camera optics is therefore required. Automatic interlocks disable the infrared video camera when the flash exposure is made. One Polaroid photograph was taken of the right eye, centred on the fovea and including areas lateral to the macula and nasal to the disc, and both superior and inferior temporal arcades. After 2 to 5 minutes (to allow the pupils to dilate after the first flash) the left eye was also photographed. The use of Polaroid pictures enabled rephotography if their quality was inadequate. A record was made of the patient's reaction to the flash.

One drop each of phenylephrine 10% and tropicamide 1% was then instilled into both eyes. When the pupil was fully dilated, direct ophthalmoscopy was performed by an ophthalmologist (RM) without knowledge of the photographic findings. Details of the fundus examination were systematically recorded. Any retinopathy was assessed for severity of haemorrhages plus microaneurysms, hard exudates, cotton-wool spots, venous abnormalities, intraretinal microvascular abnormalities (IRMA), new vessels (both on the disc and elsewhere), and fibrous tissue (on the disc and elsewhere). Each type of lesion was judged against transparencies from the Early Treatment of Diabetic Retinopathy Study standard photographic slides,[3] which were placed on an adjacent radiographic viewing box, to facilitate comparison. For the purpose of this report retinopathy was considered to be minimal if only one to five microaneurysms and not more than one haemorrhage were present; mild if there were other lesions such as haemorrhages and hard exudates, but not requiring photocoagulation; maculopathy if there were haemorrhages and exudates in the perifoveal area and marked discolouration of the fovea; and proliferative if there were new vessels on the disc, and/or in the retinal periphery, and photocoagulated if there were scars of photocoagulation or the patient gave a history of laser treatment.

The photographs were coded and assessed in a 'blind' manner by EMK for the presence and severity of retinopathy and for photographic quality. This was undertaken twice, in random order, and at least two weeks apart. Assessment of retinopathy was also by comparison with the ETDRS standard slides. Oedema formation or retinal elevation could not be graded because stereo photographs were not available. Photographic quality was assessed on an arbitrary scale from 1 to 5, 1 being excellent, 2 good and easily assessable, 3 assessable with some difficulty, 4 only part of the field assessable, and 5 unassessable.

Table 2 *Visual acuity in Indian and European eyes*

	Indian	*European*
6/6	44	32
6/9	18	20
6/12	1	4
6/18	9	8
6/24	0	3
6/36	2	4
6/60	0	1
Worse than 6/60	12	6

The study was approved by the Ealing Hospital Ethical Committee. Student's t test and χ^2 tests were used for statistical comparisons.

Results

VISUAL ACUITY

Visual acuities of 43 Indian patients were obtained. Only one patient was blind in both eyes, and most had good vision (Table 2). There were only 12 eyes with a visual acuity less than 6/36, and only five patients with vision worse than 6/9 in both eyes.

Visual acuities of 39 European patients were obtained. No patient was blind in both eyes, but two patients had only 6/36 vision in their better eye. Impaired visual acuity occurred with similar frequency in the two ethnic groups.

OPHTHALMOSCOPIC FINDINGS

The ophthalmoscopic assessments are detailed in Table 3 and summarised in Table 6. In Indian patients retinopathy was present in 41 eyes and absent in 40 eyes; nine fundi (in seven patients) could not be adequately assessed because of cataract formation. In European patients retinopathy was present in 45 eyes, absent in 31 eyes, and four fundi (in three patients) could not be adequately assessed. There was no significant difference in the presence of severity of retinopathy between the two ethnic

Table 3 *Assessment of retinopathy by ophthalmologist*

	Indian eyes	*European eyes*
No retinopathy	40	31
Minimal	10	14
Mild	16	13
Maculopathy	8	5
Maculopathy (in spite of PC*)	–	5
New vessels (no PC)	–	1
New vessels (in spite of PC)	3	2
PC now mild retinopathy	2	1
Outside standard fields†	2	4
Not assessable	9	4

*PC=photocoagulation.
†Retinopathy outside 45° photographic field only.

Table 4 *Photographic quality*

*Grade**	*Indians*		*Europeans*	
	1st reading	*2nd*	*1st reading*	*2nd*
1	29	31	25	28
2	24	26	24	23
3	18	13	15	13
4	9	10	11	10
5	6	6	4	5

*See text for definitions of photographic quality grading system

groups. Most patients with retinopathy had minimal or mild lesions only. New vessels were present in five eyes despite previous photocoagulation, and also in one eye which had not been treated. Five eyes had persistent extensive hard exudates despite previous treatment.

PHOTOGRAPHIC QUALITY

Photographs were taken of 165 out of 170 eyes (86 Indian and 79 European). Their quality was assessed as either excellent or good (grades 1 or 2) in 105 (64%) (the mean of two readings). However, 6% of photographs were totally unassessable (grade 5) and a further 12% were only partially assessable (grade 4). The poor quality photographs were evenly distributed between the two ethnic groups (Table 4) and throughout the three months of the study.

WITHIN OBSERVER VARIATION

There was agreement between first and second readings on the presence or absence of retinopathy in 158 of 165 eyes, a 96% reproducibility (Table 5). The seven photographs producing different readings were of patients (four Indians and three Europeans) adjudged to have minimal retinopathy on one reading and none on the other. There was also excellent agreement between the first and second assessments of the severity of retinopathy. The concurrence between first and second readings was similarly good in Indian and European eyes.

Table 5 *Photographic assessment*

Retinopathy grading	*Indians*		*Europeans*	
	1st reading	*2nd*	*1st reading*	*2nd*
None	26	30	29	26
Minimal	17	13	16	19
Mild	17	17	16	16
Maculopathy	7	7	8	8
NVD/NVE*	0	0	1	1
PC†+NVD/NVE	4	4	0	0
PC+mild or minimal	3	3	2	2
Unassessable	11	11	7	7

*NVD/NVE=new vessels on the disc, and new vessels elsewhere
†PC=photocoagulation.

Table 6 *Comparison of photographic and ophthalmological assessment of retinopathy*

		Ophthalmological assessment			
		Present	*Absent*	*Unassessable*	*Total*
Europeans					
Photographic assessment	Present	34	9	0	43
	Absent	8	21	0	29
	Unassessable	3	1	3	7
	Totals	45	31	3	79
Indians					
Photographic assessment	Present	35	15	1	51
	Absent	3	22	1	26
	Unassessable	3	2	4	9
	Totals	41	39	6	86

Among the European patients there were 34 eyes which had retinopathy on both ophthalmological and photographic assessment. In nine eyes the ophthalmologist found no lesions, while there were some found on the photographs. There were eight occasions when retinopathy was found on examination by the ophthalmologist but not on photography

In 21 eyes neither the ophthalmologist nor the photographic grader found lesions There were three photographs judged unassessable when the ophthalmologist found lesions and one where the photograph was unassessable when no lesions were found by the ophthalmologist. Finally there were three eyes that could not be assessed by the ophthalmologist, and their photographs were also unassessable

The findings of the Indian patients' eyes can be interpreted in a similar fashion

COMPARISON OF OPHTHALMOLOGICAL AND PHOTOGRAPHIC GRADING

There was concurrence between the ophthalmological and photographic assessments of the presence or absence of retinopathy (and its assessability) in 61 (71%) of 86 Indian eyes and 58 (73%) of 79 European eyes (Table 6). There was no disagreement between the two assessment methods on clinically significant macular lesions, new vessels, or previous photocoagulation. The overall concurrence was 119 of 165, or 72%. There were 21 disagreements in European eyes, of which eight were reported to have retinopathy by the ophthalmologist alone. In four of these cases the lesions were outside the photographic field, and the other four had minimal lesions only. Of the nine European eyes reported to have retinopathy by the photographic reader alone three were considered to have mild and six minimal retinopathy. The 25 disagreements on Indian eyes included 15 adjudged to have minimal or mild retinopathy on photographic assessment alone. In one of the three Indian eyes reported to have retinopathy by ophthalmoscopy alone the lesions lay outside the photographic field.

DISCOMFORT OF PHOTOGRAPHS

Thirteen Indian and two European patients experienced some discomfort during the photographs, and four Indians thought it sufficient to decline yearly examination. Two of these photographs were partially or totally unassessible (grade 4 or 5), but in the other two their quality was good. Only one of the four had cataracts.

Discussion

The early recognition of diabetic retinopathy is vitally important because it is now a treatable condition. However, there is no consensus on which method of screening (whether ophthalmoscopy by physicians, ophthalmologists, or opticians, or by use of the non-mydriatic fundus camera) is most suitable for general use. This study highlights some advantages and disadvantages of the camera. It is broadly comparable to ophthalmoscopy through dilated fundi by an ophthalmologist in detecting retinopathy, in determining its severity, and in enabling patients to be selected for further investigation and consideration of laser treatment. It is almost certainly superior to ophthalmoscopy by physicians working in busy diabetic clinics,[4] especially if performed through undilated pupils. However, consultant ophthalmologists would not undertake routine screening of all diabetic patients because of the time involved, though clinical assistants could perhaps be trained for this task.

Unfortunately there are also some significant drawbacks. Firstly, a proportion of photographs are technically unsatisfactory. In this study 6% were unassessable and an additional 12% only of limited use. These figures are broadly similar to those of previous studies.[1 2] Difficulties in obtaining satisfactory photographs are more likely to occur in patients who have cataracts or are elderly. Many such patients may not attend a hospital clinic, and an adequate photographic assessment would therefore be vital in community use. Furthermore, if a poor picture were obtained, it would be difficult for a photographic technician to decide the cause, the urgency of referral, and whether the patient should be referred to a diabetic clinic or to an eye clinic for consideration of cataract extraction.

Secondly, the camera will fail to detect lesions which lie outside the photographic field. In our study this occurred in two of 86 Indian eyes and in four of 79 European eyes. Klein *et al.* have suggested that retinopathy may lie outside the photographic field in 8–15% of cases.[5] Thirdly, neither direct ophthalmoscopy nor a single retinal photograph are adequate to screen for macular oedema. This is a significant defect of both screening methods because of the findings of the Early Treatment of Diabetic Retinopathy Study that early macular oedema with normal or near normal vision benefits most markedly from treatment.[6] Many patients would require referral for either stereo photography or fluorescein angiography to ensure that they are treated at an early stage when vision can be maintained. Fourthly, some patients found the photography uncomfortable, and four said that they would not consent to further photographs.

This study provides some evidence that both the prevalence and severity of retinopathy are similar in comparable groups of Indian and European diabetics. This is consistent with ophthalmoscopic findings in large unselected groups of clinic patients.[7] The prevalence of known diabetes in Indians is strikingly high, with a 5 to 7 fold increase compared with Europeans in age group 40–64 years.[8] Thus the numbers of Indians developing diabetic retinopathy which requires treatment may increase rapidly over the next few years. The fundus camera was equally suitable for use with both patient groups, though more Indians experienced discomfort with the flash. This concurs with the findings of Klein *et al.*, who found that patients with brown irises were more discomforted by the flash than patients with blue irises.[5]

The discrepancies between the ophthalmoscopic and photographic assessments are rather difficult to explain in view of a recent paper[2] which reported a virtually complete concordance between the two methods. However, the disagreements in the current study were on mild or minimal retinopathy, and many were probably due to over-reading of the photographs when in doubt, to ensure earlier re-examination of the eyes. There were no disagreements in deciding which patients required referral for further invetigation and possible treatment.

In conclusion, this study suggests that Indian diabetic patients are equally prone to developing retinopathy as comparable European patients. The Canon CR3-45NM non-mydriatic fundus camera has been validated as a reliable way of screening for retinopathy, but it has several limitations which need to be borne in mind if it is used as the only method of assessment within the community.

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Single stage insertion of the Molteno tube for glaucoma and modifications to reduce postoperative hypotony

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SUMMARY Severe glaucoma was controlled in all 13 cases following insertion of a Molteno drain in a single stage procedure. One eye required a repeat operation. A modified technique to minimise early postoperative hypotony and prevent flat anterior chambers is described

Standard filtering operations often have poor results in neovascular glaucoma,[1] other severe cases of secondary glaucoma, and in cases complicated by unfavourable factors including aphakia,[2] previous failed drainage surgery,[3 4] or the youth of the patient.[5 6] Cyclodialysis and cyclocryotherapy, techniques designed to reduce aqueous fluid production, have well recognised complications which include long term hypotony.[7 8] Both are widely regarded as giving poor visual results

The use of artificial implants to maintain aqueous fluid drainage dates from 1906.[9] In 1969 Molteno first reported his work with an implant consisting of a silicone tube attached to an episcleral plate.[10] The design was subsequently modified by lengthening the tube, allowing the plate to be sutured to the postequatorial sclera.[11] Two interconnected episcleral plates, giving a total area of 270 mm^2, have been shown to provide the optimum total bleb area In many cases of neovascular glaucoma, however, the ciliary body is severely damaged, and a single plate is therefore preferable.[12] Good results have been obtained with this system.[13–18]

Materials and methods

Patients were selected for Molteno tube surgery when medical therapy was no longer satisfactory and conventional surgery had already failed or was unlikely to have any reasonable chance of success. The eyes were divided into four groups relating to the cause of the raised intraocular pressure (Table 1). Previous intraocular surgery had been performed on eight eyes. Five eyes with neovascular glaucoma had previously received panretinal photocoagulation (Tables 2–5).

The implant consists of a silicone tube with 0·6 mm outside and 0·3 mm inside diameter attached to one or two 13 mm diameter polymethylacrylate (PMMA) plates. Single plate implants were used for cases of neovascular glaucoma.

The plates were attached and tubes inserted in a one-stage procedure. Where two plates were used, the adjoining tube was passed underneath the superior rectus muscle. The plate(s) were secured in a postequatorial position with the tube lying radial to the limbus. A large partial thickness scleral flap, hinged at the limbus, was created to cover the entire length of the tube. In some cases cover was achieved with two separate flaps. The tube length was shortened to approximately 2 to 3 mm beyond the limbus,

Table 1 *Patients receiving Molteno tube implants*

Treatment group	*Diagnosis*	*Number of eyes treated*	*Number of procedures*
I	Central retinal vein occlusion with neovascular glaucoma	4	5
II	Proliferative diabetic retinopathy with neovascular glaucoma	3	3
III	Aphakic glaucoma	3	3
IV	*Miscellaneous*		
	Coats disease/neovascular glaucoma	1	1
	Heterochromic iridocyclitis	1	1
	Post endophthalmitis/chronic angle closure	1	1
	Total	13	14

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Table 2 *Treatment group I (CRVO-NVG)*

	Age	*Sex*	*Panretinal argon laser photocoagulation*	*Preoperative visual acuity*	*Postoperative visual acuity*	*Preoperative intraocular pressure*	*Preoperative ocular medication*	*Postoperative intraocular pressure*	*Postoperative ocular medication*
1	84	M	No	CF	HM	32	Timoptol Atropine	70	
2	84	M	No	HM	CF	70	—	16	—
3	90	M	No	HM	CF	42	Timoptol Atropine	19	Timoptol
4	77	M	Yes	6/60	PL	40	—	6	—
5	74	M	No	CF	CF	26	Acetazolamide Timoptol	24	—

CRVO=central retinal vein occlusion NVG=neovascular glaucoma CF=counting fingers at 0·5 m HM=hand movements PL=perception of light

Table 3 *Treatment group II (PDR/NVG)*

	Age	*Sex*	*Panretinal argon laser photo-coagulation*	*Prior surgery*	*Preoperative visual acuity*	*Postoperative visual acuity*	*Preoperative intraocular pressure*	*Preoperative ocular medication*	*Postoperative intraocular pressure*	*Postoperative ocular medication*
1	66	F	Yes	Extracapsular cataract extraction	HM	PL	42	Acetazolamide	6	—
2	63	M	Yes	Vitrectomy and lensectomy	6/60	6/60	28	Timoptol Acetazolamide	18	—
3	69	F	Yes	Intracapsular cataract extraction, vitrectomy	CF	PL	33	Timoptol Acetazolamide	16	—

PDR=proliferative diabetic retinopathy. NVG=neovascular glaucoma

Table 4 *Treatment group III (aphakic glaucoma)*

	Age	*Sex*	*Prior procedure*	*Preoperative visual acuity*	*Postoperative visual acuity*	*Preoperative intraocular pressure*	*Preoperative ocular medication*	*Postoperative intraocular pressure*	*Postoperative ocular medication*
1	81	F	ICCE, ALT	6/5	6/9	24	Acetazolamide Timoptol	19	Timoptol
2	65	M	ICCE and IOL, ALT	6/5	6/5	28	Timoptol Pilocarpine	21	Timoptol Pilocarpine
3	69	F	ICCE	6/36	CF	24	Acetazolamide Timoptol Pilocarpine	19	Timoptol

ICCE=intracapsular cataract extraction. IOL=intraocular lens ALT=argon laser trabeculoplasty.

Table 5 *Treatment group IV (miscellaneous)*

	Age	*Sex*	*Diagnosis*	*Previous surgery*	*Preoperative visual acuity*	*Postoperative visual acuity*	*Preoperative intraocular pressure*	*Preoperative ocular medication*	*Postoperative intraocular pressure*	*Postoperative ocular medication*
1	30	M	Coats disease, neovascular glaucoma	—	PL	PL	55	—	6	—
2	52	F	Heterochromic iridocyclitis	ICCE	6/6	6/9	38	Timoptol Acetazolamide	12	—
3	71	F	Postoperative endophthalmitis	ECCE and IOL, PK, trabeculectomy	HM	HM	45	Timoptol Acetazolamide	16	—

ECCE=extracapsular cataract extraction PK=penetrating keratoplasty thus allowing for postoperative tube retraction. The tube was inserted into the anterior chamber through a narrow incision and the scleral flap(s) closed securely with interrupted 8/0 virgin silk sutures. The same suture was used for the conjunctiva.

In six cases a 3/0 polypropylene suture was passed through the tube (Fig. 1). The presence of the suture, which acts as a splint, greatly facilitates the insertion of the tube into the anterior chamber. The distal end of the suture was passed over the plate, under the superior and horizontal rectus muscles, and secured to sclera (Fig. 2). The proximal end of the suture remained in the tube. Removal six weeks later, under local anaesthesia, was through a small conjunctival incision over the distal end of the suture, well away from the drainage site.

In one case the Vicryl tie procedure was employed.[19] A 6/0 Vicryl suture was tied round the tube under the scleral flap so as to occlude the lumen (Table 6).

All cases received preoperative chloramphenicol drops. The postoperative regimen was atropine drops 1% twice daily, adrenaline drops 1% three times a day, and betamethasone drops four times a day for six weeks. Adrenaline drops were not used for more than one week on intracapsular aphakic eyes. Additional systemic medication was given to four patients: group III patient 2 and group IV patients 1 and 3 were given oral prednisolone 10 mg three times a day, colchicine 0·25 mg three times a day, and indomethacin 25 mg three times a day for five weeks. In group I, patient 5, unable to tolerate the full regimen, was given oral prednisolone 10 mg three times a day for three weeks.

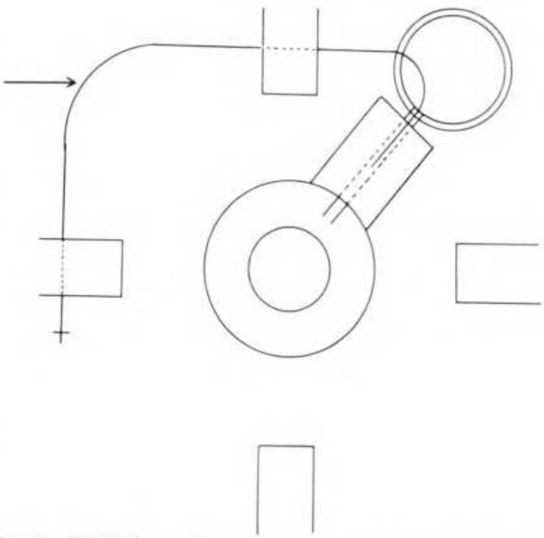

Fig. 2 *3/0 Polypropylene suture (arrow) is inserted half way down the Molteno tube, passed under the superior and horizontal rectus muscles, and secured to sclera.*

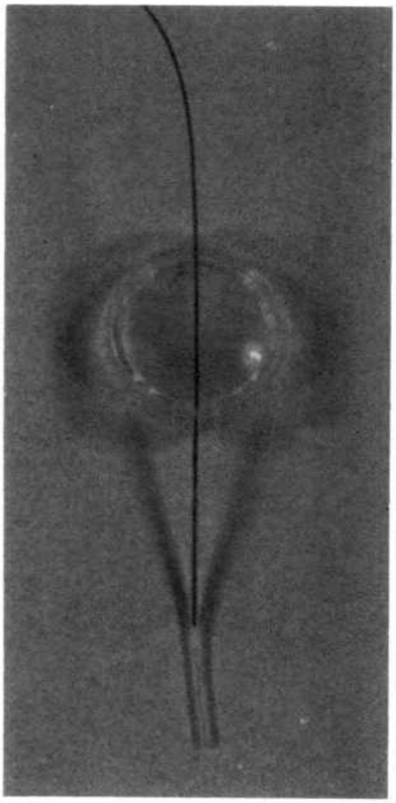

Fig. 1 *Single plate Molteno tube with 3/0 polypropylene suture.*

Results

Tables 2–5 show that all cases, with the exception of case 1 in group I, achieved an intraocular pressure less than 25 mmHg. The mean fall in pressure was 23 mmHg. Four eyes, three of which had aphakic glaucoma, required additional antiglaucoma drops. The mean follow-up was 14 months, with a range of 6 to 27 months. In group I patient 5 died three months after the operation. All eyes retained vision, seven eyes showed a small deterioration, and two eyes a

Table 6 *Operative procedures*

Procedure	*Number*
Single plate Molteno tube	7
Single plate and 3/10 Prolene	3
Double plate and 3/0 Prolene	3
Double plate and Vicryl tie procedure	1

Table 7 *Postoperative complications*

Procedure	*No*	*Hyphaema*	*Vitreous haemorrhage*	*Vitreous face opacification*
Open tubes	7	7	–	–
Tubes with 3/0 Prolene	6	5	1	2
Tube with Vicryl tie	1	1	–	–

Table 8 *Postoperative complications*

Procedure	*No.*	*Hypotony*	*Flat AC*	*Choroidal detachment*		*Corneal touch*	
				Early	*Pers*	*Early*	*Pers.*
Open tubes	7	4	4	2	1	4	1
Tubes with 3/0 Prolene	6	3	–	1	–	2	–
Tube with Vicryl tie	1	–	–	–	–	1	–

AC=anterior chamber Pers =persistent.

small improvement in visual acuity. There were no cases of infection.

Case 1 in group I developed profound hypotony, with choroidal detachment and a flat anterior chamber, after insertion of a single plate tube without an intraluminal 3/0 polypropylene suture. On the fourteenth day iris occluded the tube, resulting in a sharp rise in intraocular pressure. Attempts to clear the tube failed. The original implant was removed, and a single plate tube with a 3/0 polypropylene suture was inserted at a fresh site (recorded as group I case 2). Transient obstruction by iris was observed in one other case without a 3/0 polypropylene suture.

In the first case where the polypropylene was used postoperative retraction of the Molteno tube resulted in protrusion of the suture into the anterior chamber (case 2, group III). This required adjustment under local anaesthesia on day 4. In all subsequent cases the polypropylene sutures were withdrawn half way up the tube, before they were secured to the sclera, at the time of the initial operation. Other complications are summarised in Tables 7 and 8. Hypotony, defined here as an intraocular pressure less than 2 mmHg, was found in the early postoperative phase in seven eyes. Five of these eyes had neovascular glaucoma. Associated flat anterior chambers were found in four eyes, all with open tubes. No flat anterior chambers were found in eyes where the suture had been placed in the tube. One case of choroidal detachment and one case of corneal touch persisted beyond 10 days, both in eyes with open tubes.

During the first eight postoperative weeks there were six cases of raised intraocular pressure. The maximum reading was 35 mmHg, and all returned to normal by the end of this period. In two cases the polypropylene suture was removed early, at three weeks, in each case producing a significant drop in pressure (group I, patient 4, and group IV, patient 2).

Postoperative hyphaema was present in 12 eyes, and all cleared in the first fortnight. There were no cases of obstruction of the tube with blood clot.

The two cases of vitreous face opacification occurred in the aphakic glaucoma group (group III, patients 1 and 2). In both cases treatment with the YAG laser resulted in vitreous entering the tube causing a rise in intraocular pressure. In patient 2 partial clearance was obtained with further YAG laser applications to the vitreous within and adjacent to the tube. Control of the intraocular pressure was regained with the use of additional topical treatment.

Discussion

In the absence of surgical damage to the ciliary body postoperative hypotony is often a consequence of continued excessive escape of aqueous fluid. In a series of 30 single-plate Molteno tubes, inserted in a one-stage procedure, seven flat anterior chambers were reported in the first postoperative week and one of these resulted in failure.[14] In this series four out of 13 eyes had flat anterior chambers in the first week, and all achieved a satisfactory final result.

Obstruction of the tube by iris or vitreous occurring after single-stage insertion has been described and associated with excessive aqueous drainage.[11 14] In this series two cases of obstruction by iris coincided with hypotony, and in one case this caused a serious rise in intraocular pressure, necessitating a repeat operation. Interestingly our two cases of vitreous entry into the tube occurred after YAG laser treatment, a previously unrecognised complication of this procedure.

Molteno advocates insertion of the tube in a two-stage procedure, permitting a thin layer of fibrous tissue to surround the plate, thereby creating some resistance to the passage of aqueous fluid. Good results were obtained, and the technique also reduced the incidence of hypotony and secondary obstruction of the tube with iris or vitreous.[11] There are, however, two main disadvantages with a two-stage procedure: the condition of the eye may not permit such a delay and two major operations are required.

One alternative is temporarily to occlude the lumen of the tube by tying an absorbable suture round the outside. With a single loop of 5/0 Vicryl suture the tube has been shown to open up after an average of four weeks, with a few cases possibly taking up to eight weeks. Good results have been reported with this method.[19] Molteno *et al.* have reported that, with a 22 gauge needle for entry into the anterior chamber, leakage of aqueous fluid outside the occluded tube ceased a few minutes after insertion. Continued treatment with glaucoma medication was required until the tube reopened. This method has successfully eliminated the necessity of a second-stage operation, but the problem of potential delay in adequate control of intraocular pressure still remains.

The technique we have used in an attempt to overcome these problems is temporarily to partially occlude the lumen of the Molteno tube by inserting 3/0 polypropylene down its length. The presence of the suture, while permitting the flow of some aqueous fluid, greatly reduces the overall drainage and, if required, could be used to clear any obstruction of the tube by iris, vitreous, or blood. The intention is to provide immediate control of intraocular pressure, without profound hypotony, with simultaneous limited deposition of fibrous tissue round the episcleral plate. The polypropylene, acting as a splint, also facilitates insertion of the tube into the anterior chamber at the time of operation.

The numbers in the study are too few to demonstrate conclusively a modifying effect of the intraluminal 3/0 polypropylene suture. These first results, however, suggest that hypotony may be mitigated but not prevented. Aqueous drainage outside the tube is unaffected by the suture, and despite a narrow anterior chamber incision we believe in some cases contributes to the lowering of the intraocular pressure in the early postoperative phase. Hypotony is therefore not eliminated. In contrast to the open tubes, however, no flat anterior chambers were observed with the 3/0 polypropylene suture. In the two cases of early suture withdrawal a fall in intraocular pressure was observed, demonstrating an increase in aqueous flow. It is probable that a more complete fibrous lining to the bleb accounts for the absence of a pressure drop on withdrawal at six weeks.[13]

The histology of functioning and failed blebs is well recognised.[11 20-25] Evidence exists for a role of aqueous fluid in fibroblast growth in tissue culture and in bleb fibrosis.[26-28] In a monkey model aqueous aspirated from eyes that had previously undergone filtration surgery supported growth of tissue cultures of subconjunctival fibroblasts. This ability to support growth diminished with increasing postoperative interval. 92% of cultures were positive with aqueous samples removed at one week, 75% at four weeks, and 33% at eight weeks.[27] This duration is similar to the period of postoperative bleb inflammation and associated increased intraocular pressure observed by Molteno *et al.*[28]

To minimise excessive bleb fibrosis Molteno advocates the use of a long tube in a two-stage or Vicryl tie procedure together with administration of oral prednisone, fluphenamic acid, and colchicine.[11 13 19 29 31] Brown and Cairns did not find improved results in patients given this systemic medication.[30] In our series four patients received oral enteric coated prednisolone, indomethacin, and colchicine The full regimen was tolerated in three of these patients. The numbers at this stage are too small to demonstrate the effect on final results.

Other studies to assess pharmacological modification of drainage surgery have been undertaken. In a randomised prospective trial, which excluded patients with aphakia or previous drainage surgery, Starita *et al.* showed the success rate of trabeculectomy to be improved by topical steroids, with no additional benefit from systemic steroids.[32] Topical indomethacin has been shown to have an adverse effect.[33] Fourteen out of 15 eyes with increased risk of filtration failure had successful trabeculectomies following preoperative subconjunctival triamcinolone.[34] The place of 5-fluorouracil, while the drug appears to be potentially useful, remains to be established.[35-38] The results of further studies on animals and humans are awaited.

Encouraging results, without the use of systemic medication, have been obtained with a tube attached to an encircling band.[39 40] Schocket *et al.* point out that success depends on the formation of scar tissue. Fourteen out of 30 eyes in their series had flat anterior chambers and, significantly, all had neovascular glaucoma.[39] Drainage into a large surface area with a one-piece system incorporating a valve has been reported to have a much lower incidence of flat anterior chamber.[41]

The optimum early postoperative aqueous fluid flow rate and the optimum ratio of drainage area to fibrous well thickness, for tube systems used in glaucoma, remain to be determined.

We believe the results of single-stage insertion of the Molteno tube and the temporary presence of an intraluminal suture are encouraging.

While the use of the systemic antifibrosis regimen is inconclusive in this study, we accept that there is a need for vigorous suppression of inflammation and fibrosis in some cases of Molteno tube surgery.

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A case of 'low tension glaucoma' with primary empty sella

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SUMMARY A case of 'low tension glaucoma' with primary empty sella is reported. The visual field defect and optic disc change were characteristic of glaucoma. The intraocular pressure was within normal limits. *X*-ray examination and the metrizamide-CF procedures revealed a primary empty sella. The coexistence of 'low tension glaucoma' and empty sella is discussed.

The term 'empty sella' was introduced by Busch[1] and applied to the appearance of the sella turcica in which the diaphragma sellae is incomplete and the pituitary gland appears to be absent anatomically. It is divided into two categories—primary (without prior surgical or radiotherapeutic procedures) and secondary (following such procedures).[2] The latter type is reported to show a variety of visual disturbances.[3,4] On the other hand the former type is associated with few ophthalmological dysfunctions.[5,6]

We report a patient with glaucoma-like optic disc changes and visual field defects coexisting with the primary empty sella syndrome. And we also draw attention to the need for neurological examinations when we encounter 'low-tension glaucoma'.

Case report

A 70-year-old woman (height 149 cm, weight 44·6 kg) was referred to us in February 1986 by her family doctor. She had no history of radiotherapy, intracranial operations, hypertension, or diabetes mellitus, but she had had mild bifrontal headaches from before the age of 10 years. Her menstrual periods occurred from age 14 to 44 years, but were sometimes irregular, with abnormally large haemorrhages occasionally. Her two daughters gave no history of glaucoma, optic nerve disease, or intracranial disease. Her other relatives were likewise healthy.

The patient's corrected visual acuities were 1·0 in the right eye and 0·8 in the left. Her eye movements were normal in all directions. The pupils were round and of equal size. Direct and indirect light reflexes were brisk, and the swinging flashlight test gave normal results. The anterior segments of both eyes were normal on slit-lamp examination except for incipient cataract (anterior and posterior subcapsular). The right optic disc showed glaucomatous excavation, with a C/D ratio 95%, and the left disc had glaucomatous excavation, with a C/D ratio 85%. The superior and inferior rims were narrower than the temporal and nasal rims. The lamina cribrosa was clearly visible in both eyes (Fig. 1). Applanation tension was RE, 14 mmHg, LE, 16 mmHg. The facility of outflow was 0·24 μl/min/mmHg RE and 0·30 LE. Gonioscopically the chamber angles were wide open in both eyes. Perimetry with Goldmann and Humphrey perimeters showed a nasal upper visual field defect in the left eye and a nasal upper quadrant defect in the right eye (Fig. 2). A 100-hue colour test showed error scores of 45, and the pattern electroretinogram (ERG) showed a good response. The diurnal profile (every two hours) of intraocular pressure ranged from 12 to 16 mmHg in the right eye and from 13 to 17 mmHg in the left eye (Fig. 3). Central critical flicker value showed 45–50 cycle/s in both eyes.

X-ray examination of the skull showed an oval configuration and increased volume of the sella turcica (Fig. 4). The length of the sella turcica was 17 mm, the depth 15 mm, the width 22 mm, and the volume 2187 mm^3. The lumbar cerebrospinal fluid gave a pressure 120 mm H_2O opening pressure. The fluid contained no cells and the concentration of protein was normal. By metrizamide computed

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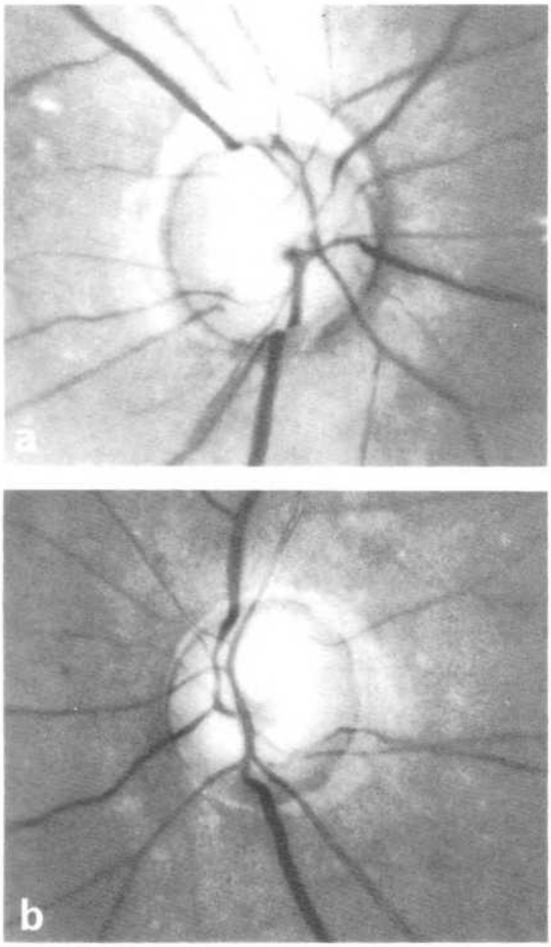

Fig. 1 *Fundi of both eyes. Note typical glaucomatous cupping. These photographs were taken with a green filter.* a: *Disc of right eye. C/D=95%.* b: *Disc of left eye. C/D=85%.*

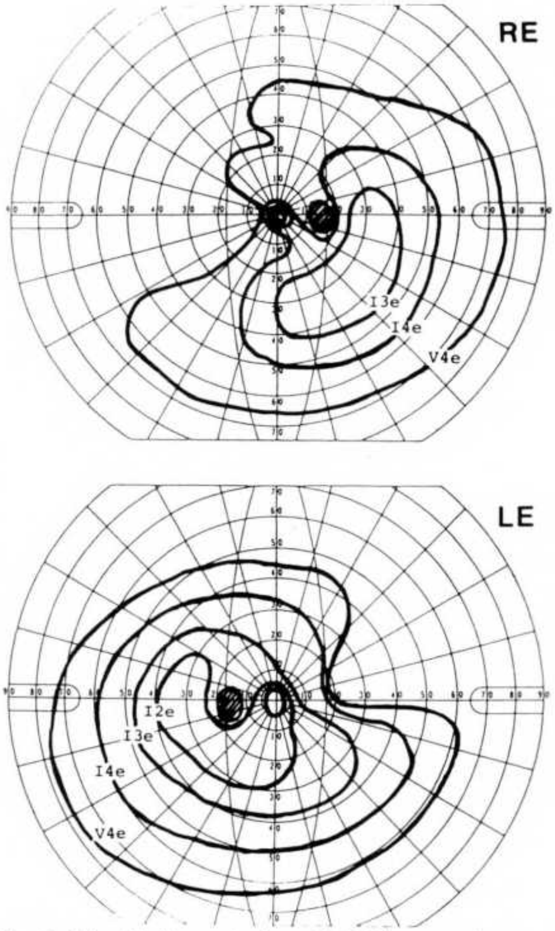

Fig. 2 *Visual field examination with Goldmann perimeter. Note the defect in both upper nasal quadrants.*

tomography (CT) the sella turcica showed high density absorption (Fig. 5).

The patient was followed up without any treatment for one year. There was no progression of the optic disc changes or visual field defects.

Discussion

Some differences of opinion exist on the criteria for the diagnosis of low tension glaucoma. Our diagnostic criteria for low tension glaucoma are as follows: (1) the presence of glaucomatous changes in the optic disc and visual field; (2) normal IOP, which means that the diurnal curve of the IOP never exceeds 21 mmHg; and (3) no systemic or ocular disease causing the optic nerve changes. Our case raises the question of low tension glaucoma or pseudoglaucoma. The coexistence of an empty sella with a glaucomatous optic disc and visual field changes without a high IOP is discussed below.

Most cases of primary empty sella do not show conspicuous disturbances of the visual field, but there have been a few cases with glaucoma-like field defects. Berke[5] reported two cases with a visual field defect among 19 cases of primary empty sella; one case had a right homonymous hemianopsia and the other case had a right temporal upper defect. These cases showed no glaucomatous changes in the discs. Okamoto and associates[7] reported a case with unilateral central scotoma as is seen in retrobulbar neuritis.[7] Nakajyo and associates[8] reported a case with bitemporal upper quadrant field defect, but there was no abnormality of the disc. On the other hand Neelon *et al.*[4] reported a case with a slight defect in the periphery of both nasal and temporal superior fields from 31 primary cases of empty sella, which his

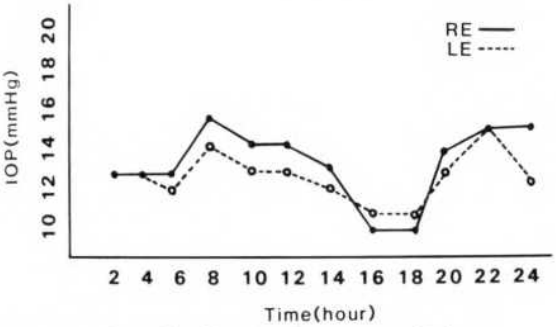

Fig. 3 *Daily profile of intraocular pressure which was checked every 2 hours.*

consulting perimetrist thought to be probably within the normal range. Shinoda and associates[9] reported two cases with nasal defects; one case showed slight temporal pallor of discs and the other case showed moderate concentric disc cuppings, but there were no ophthalmological changes diagnostic of glaucoma.

On the other hand the secondary empty sella differs in its symptomatology from the primary empty sella syndrome. Jordan *et al.*[10] reported three cases of secondary empty sella with visual field defects. The first case showed a bitemporal defect, the second a right temporal defect, and the third a left temporal and right central scotoma.[10] Shinoda *et al.*[9] described an enlargement of the Mariotte blind spot and both choked discs in a case of the secondary type following meningitis. According to previous reports the defects tend to occur in the temporal field. Moreover, even if it showed glaucomatous visual field defects, no definite glaucomatous optic disc changes have been reported so far.

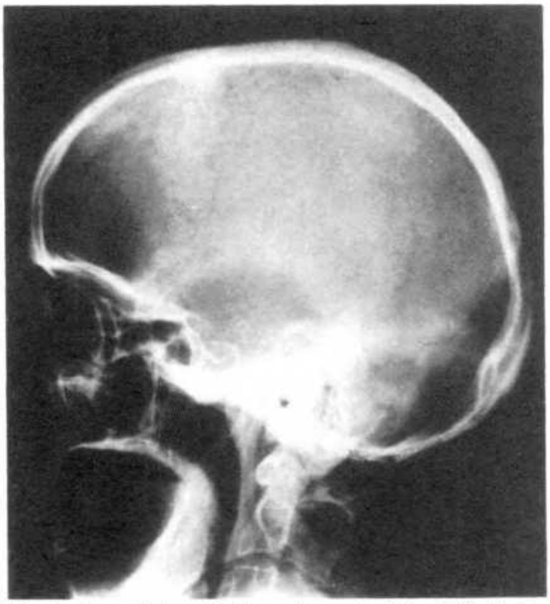

Fig. 4 *Lateral view of plain radiograph of the skull. Note ballooning of the sella turcica.*

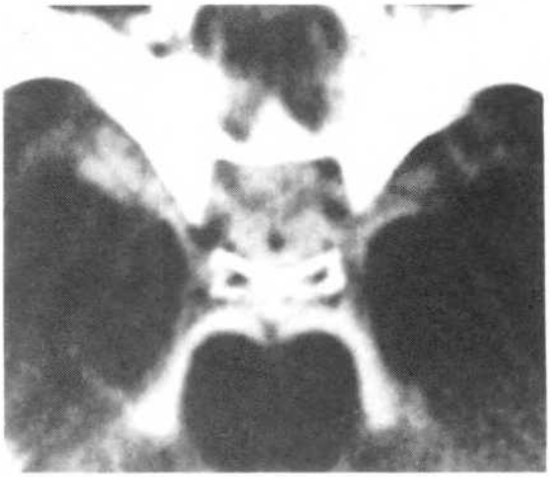

Fig. 5 *Metrizamide-CT shows high absorption into sella turcica.*

Two mechanisms are supposed to be related to the pathogenesis of optic nerve change in the empty sella syndrome. One is mechanical traction and the other vascular ischaemia. According to Bergrand and associates[11] the nerve fibres in the optic chiasm are perfused from the posterior communicating arteries, and these arteries pass round the infundibulum above the pituitary gland and also perfuse this area. Therefore, if some mechanical changes occur near the pituitary or the sella turcica, firstly the arachnoid may be drawn inferiorly and the optic chiasm may be pulled downward at the same time; secondly, these perfusion vessels are also retracted, with resultant ischemic changes in the optic nerve. Okamoto *et al.*[7] mentioned about the arachnoiditis of the optic chiasm as another factor which produces field loss. In their view loss of visual field is usually caused by vascular strangulation. Meanwhile, postoperative adhesion and postirradiation vasculitis may cause delayed atrophy of the optic nerve and chiasm in secondary empty sella syndrome.[3]

Neurological diseases affecting the optic nerve or chiasm should always be considered before making a definite diagnosis of low tension glaucoma, since they may produce visual field defects that can be confused with glaucomatous changes. In the present case a nasal field defect and glaucomatous disc changes were observed. A question remains whether these changes are related to glaucoma or to the empty sella. There are two possible explanations, one is that the two diseases occurred independently by chance—that is, the diagnosis is low tension glaucoma—and the other is that the two diseases are related to each other—that is, the diagnosis is pseudoglaucoma. If the latter is true, this case may explain the pathogenesis of at least some cases of glaucomatous optic atrophy.

Pneumoencephalography has been used to diagnose the empty sella syndrome, but this procedure may have some complications. In the present case metrizamide-CT was used to define the empty sella. This agent is a radiopaque derivative from a benzamido and a glucopyranose and very soluble in water. The procedure is simpler than pneumoencephalography and side effects are less common.[9,12]

This case suggested to us that a complete examination for intracranial diseases is necessary in case of low tension glaucoma. The clinical diagnosis of empty sella is thought to be very difficult by plain radiography and some cases need to be examined by metrizamide-CT. Therefore, if we can apply this procedure in all cases of low tension glaucoma, more cases of empty sella will be found.

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Spontaneous reformation of upper eyelid

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SUMMARY Twenty-six patients with lesions of upper eyelids were treated with simple surgical excision under local anaesthesia as day cases. Three other patients with eyelid injuries had full-thickness margin-inclusive lacerations of upper eyelids. In all these 29 patients the upper eyelid wounds were allowed to heal solely by spontaneous repair. The cautious study began with small extramarginal skin excisions and progressed gradually via moderate sized juxtamarginal excisions of skin and orbicularis lamella to full-thickness margin-inclusive excisions. The wounds healed satisfactorily in all the 29 patients without ocular or palpebral complications. The functional results were normal. Cosmetic results were excellent in 27 patients and acceptable in 2, one of whom subsequently underwent a secondary oculoplastic repair. This study demonstrates that, for upper eyelids, full-thickness margin-inclusive excisions of up to 10 mm in horizontal extent and 5–6 mm in height, and moderate sized 13×10 mm juxtamarginal excisions of the skin and orbicularis lamella, yield near normal results with solely spontaneous repair. Immediate surgical reconstruction of such wounds is assumed to be mandatory by current tenets of oculoplastic surgery.

For the *lower* eyelids, it has been established that full thickness margin inclusive (FTMI) excisions of up to 12 mm in horizontal and 5–6 mm in vertical extent yield near normal results even if allowed to heal solely by spontaneous repair.[1] The response of the upper eyelid wounds to spontaneous repair was unknown. It was therefore decided to undertake a study for such an assessment. Because of the complications of corneal and conjunctival exposure from a coloboma resulting from a surgical malrepair of an upper eyelid, a very cautious approach was designed for this study. Initially, small *extramarginal* superficial lesions of the skin of the upper eyelid were allowed to heal by spontaneous repair after a 'skin-only' horizontal excision of 6×4 mm. This gave satisfactory, uncomplicated results in all four patients. Therefore in the next two patients larger and deeper extramarginal excisions including the skin and orbicularis were so treated. After uneventful, satisfactory results in both these patients the study was extended to small shallow FTMI excisions of 6×3 mm. It was then decided to evaluate the results of solely spontaneous repair of upper eyelids after: (1) larger excisions of the skin and orbicularis lamellae at the lid margin, (2) larger FTMI excisions of 8 mm or more in horizontal and 4–5 mm in vertical extent, and (3) FTMI lacerations of injured eyelids. The results obtained in 29 patients are presented here.

Patients and methods

Twenty-nine patients with lesions of upper eyelids treated between 1979 and 1986 were included in this study. The youngest patient was 12 and the oldest 97, with an average age of 67 years. Eight patients were aged 50 years or less. The maximum follow-up period was 7½ years, and the minimum 6 months, the average observation being 42 months. In six patients the follow-up was under 12 months, and 19 patients have been observed for over three years. As the incidence of rodent ulcers and other malignancies of the upper eyelids is much lower than that for the lower eyelid, patients requesting or needing excisions of not only suspected malignant lesions but also clinically benign unsightly nodules (other than meibomian cysts and styes) that would have conventionally been treated by excision and primary surgical repair are included in this unselected study. Four patients with trichiasis, three of whom had recalcitrant trichiasis despite previous electrolysis, were managed by FTMI excision of the strip bearing aberrant eyelashes. Three patients with FTMI lacerations of injured upper eyelids were also managed with spontaneous repair.

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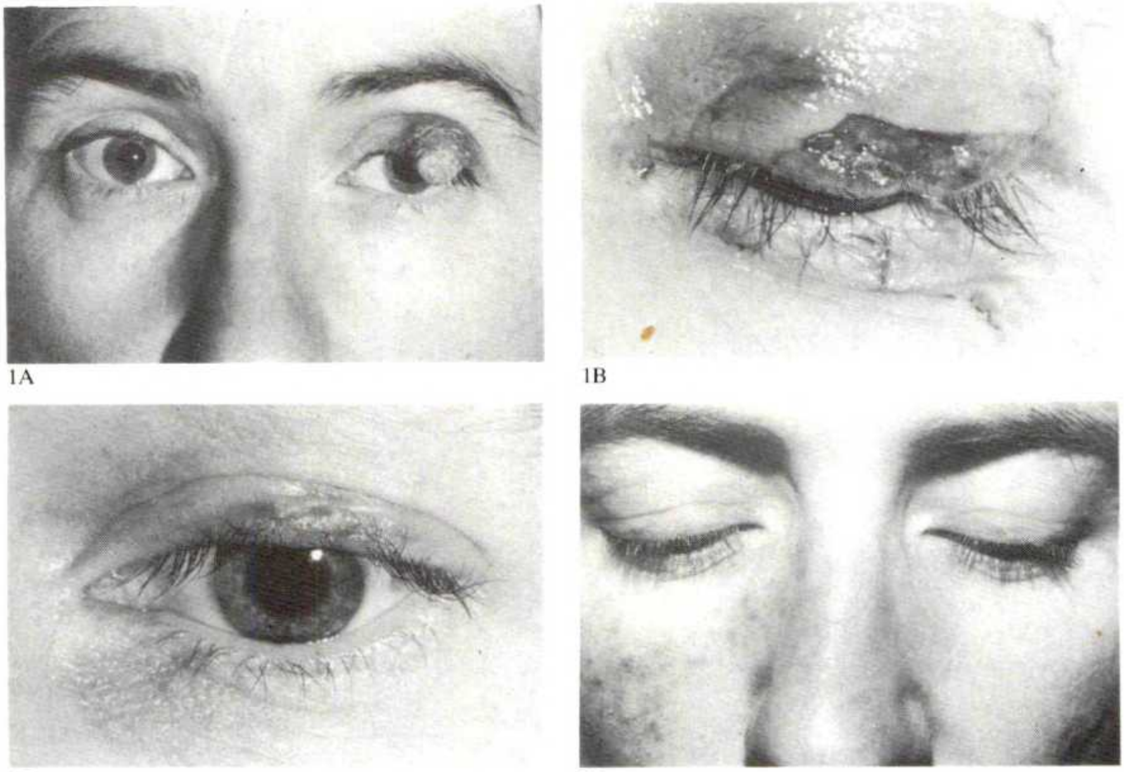

Fig. 1 (A) *Cutaneous horn of upper eyelid. Excision carried out under local anaesthesia as a day case. Immediate postoperative picture of a 13 mm × 10 mm excision of orbicularis and skin lamella is unavailable. Wound allowed to heal by spontaneous repair.* (B) *Appearance 48 hours postoperatively shows rapid diminution of the height of the wound.* (C) *Appearance at 4 weeks, and* (D) *final appearance of normal cosmesis. Traditionally, full-thickness skin graft would have been mandatory here.*

In the previously reported study of spontaneous repair of lower eyelids all the 11 patients were offered a choice between undergoing primary treatment by spontaneous repair or by primary reconstructive surgery.[1] Because of the impressive cosmetic and functional results of solely spontaneous repair obtained in the lower eyelids all 29 patients in this study were told that they were going to be treated solely by spontaneous repair of their upper eyelids.

These 29 patients can be classified in the following four groups: Group 1, extramarginal excisions; four patients had excision of the anterior lamella (skin ± orbicularis) for skin nodules. The largest excision was 10×6 mm. Group 2, juxtamarginal excisions; seven patients had excision of the anterior lamella extending to the margin of the eyelid. As in group 1, the excision was confined to the skin ± orbicularis muscle. The largest excision in the group was 13 mm in horizontal and 10 mm in vertical extent (Fig. 1). Group 3, full-thickness margin-inclusive (FTMI) excisions; these were carried out in 15 patients, four of whom had shallow FTMI excisions of 6×3 mm vertically for trichiasis. Of the remaining 11 patients five had FTMI excision of the upper eyelid at the inner canthus, three had excision of the central one-third of the upper lid with the largest excision being 10×6 mm vertically, and three excisions were in the intercanthal region of the lateral half of the upper eyelid (Figs. 2, 3). Group 4, traumatised upper eyelids with FTMI lacerations; there were three patients in this group. One of them had FTMI loss of eyelid tissue at inner canthus. The remaining two had full-thickness wounds of the upper eyelid involving the lid margin but without any tissue loss (Fig. 4).

SURGICAL TECHNIQUE AND MANAGEMENT

Apart from cauterisation of oozing vessels and ligation of spurting vessels with a single suture, the excision was the sole primary procedure in 26 patients. The remaining three patients had traumatic FTMI lacerations. They did not need surgical excision, but their slightly different management is

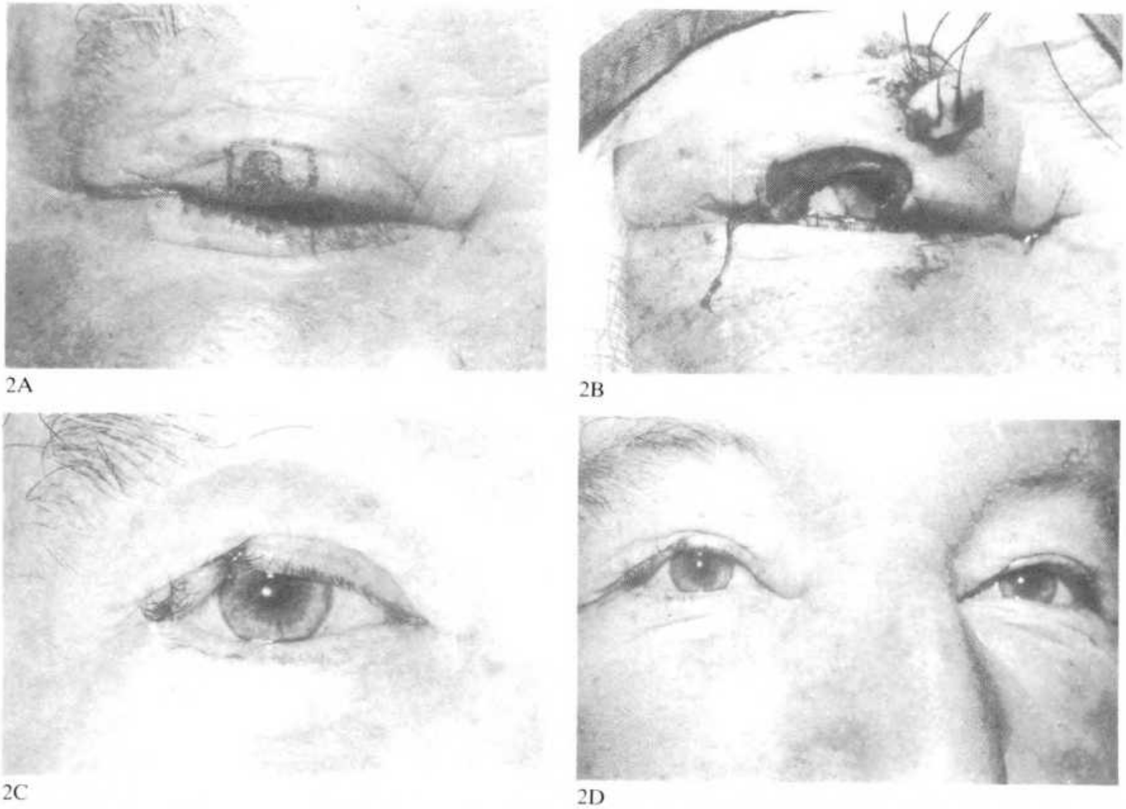
2A 2B 2C 2D

Fig. 2 (A) *Preoperative appearance of rodent ulcer at lid margin.* (B) *Immediate postoperative appearance of 10×6 mm FTMI excision.* (C) *Healthy wound and unaffected cornea three weeks post-operatively.* (D) *Final result at 4 months.*

explained in the legend for Fig. 4. The surgical excisions in 26 patients were carried out under local anaesthesia with lignocaine 2% and bupivacaine 0·5% with adrenaline (Marcain). The area to be excised was marked out before injecting the local anaesthetic. To achieve symmetry of clinical clearance and possibly also of the healing process, the FTMI excision was made rectangular. Whereas such symmetrical rectangular excision that included the tarsal plate was easily achieved for the lower eyelid, it was much more difficult for the upper eyelid, largely because of the 'scirrhous' consistency of its tarsal plate. The suboptimal cosmetic result of a small slanting shallow notch (Fig. 3) in one case has very probably resulted from an asymmetrical excision.

A Bard-Parker No. 15 blade was used to achieve perpendicular edges for the rectangular FTMI excisions. Small oozing vessels were cauterised and larger spurting vessels were ligated with 6-0 polyglycolic acid (Dexon) suture. Usually only one suture was necessary. To avoid corneal irritation by the suture, its ends were kept at least 2 cm long and were turned up on to the skin of the upper eyelid, where they were tethered with a separate suture of 6-0 Dexon passed through the depth of skin. Both sutures were usually removed on the seventh or ninth day. Because of greasy skin produced by the ointment neither Sellotape nor Micropore was reliable in holding down the ligating suture. The surgical excision including the ligation was usually completed within 10 minutes. Antibiotic eye ointment was instilled and a Cartella shield with an improvised hole was the sole 'dressing' for one week. The patients were allowed home within an hour of the excision. They were given cotrimoxazole (Septrin), 2 tablets twice daily for five days, and chloramphenicol eye ointment twice daily for two weeks and thereafter at night only if necessary for one more week. Patients were called for first dressing at 48 hours and then every week for four weeks, after which the follow-up period was lengthened progressively to attain six-monthly observation.

As the size of the excision was not recorded at the time of surgery, the magnitude of excision is taken as the dimensions reported in the 'Macroscopic appearance' part of the histology reports. The smallest

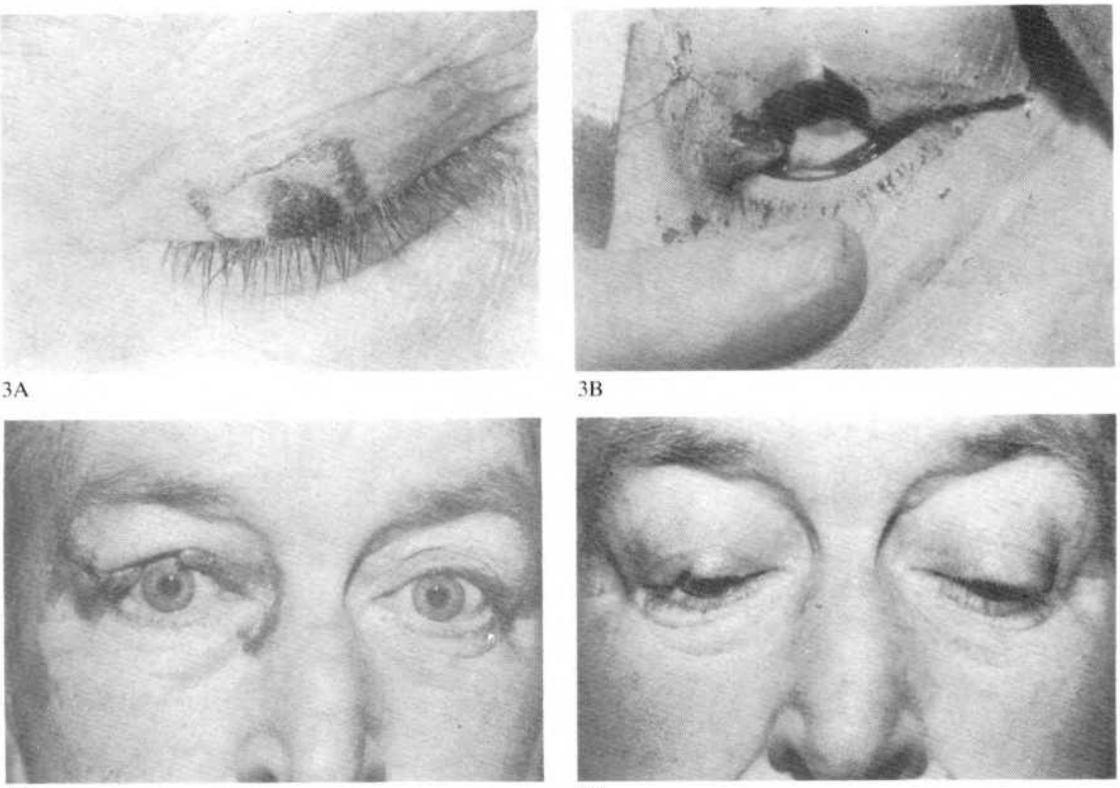

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Fig. 3 (A) *Preoperative appearance of proposed FTMI excision for a pigmented juxtamarginal lesion.* (B) *Immediate postoperative appearance shows ligating and tethering suture.* (C) *Appearance at 48 hours.* (D) *Final appearance showing a residual, small, shallow, slanting notch. Symptom-free period of three years observation.*

anterior lamellar excision was 6×4 mm and the largest was 13×10 mm. The range of FTMI excisions was 6×3 mm to 10×6 mm.

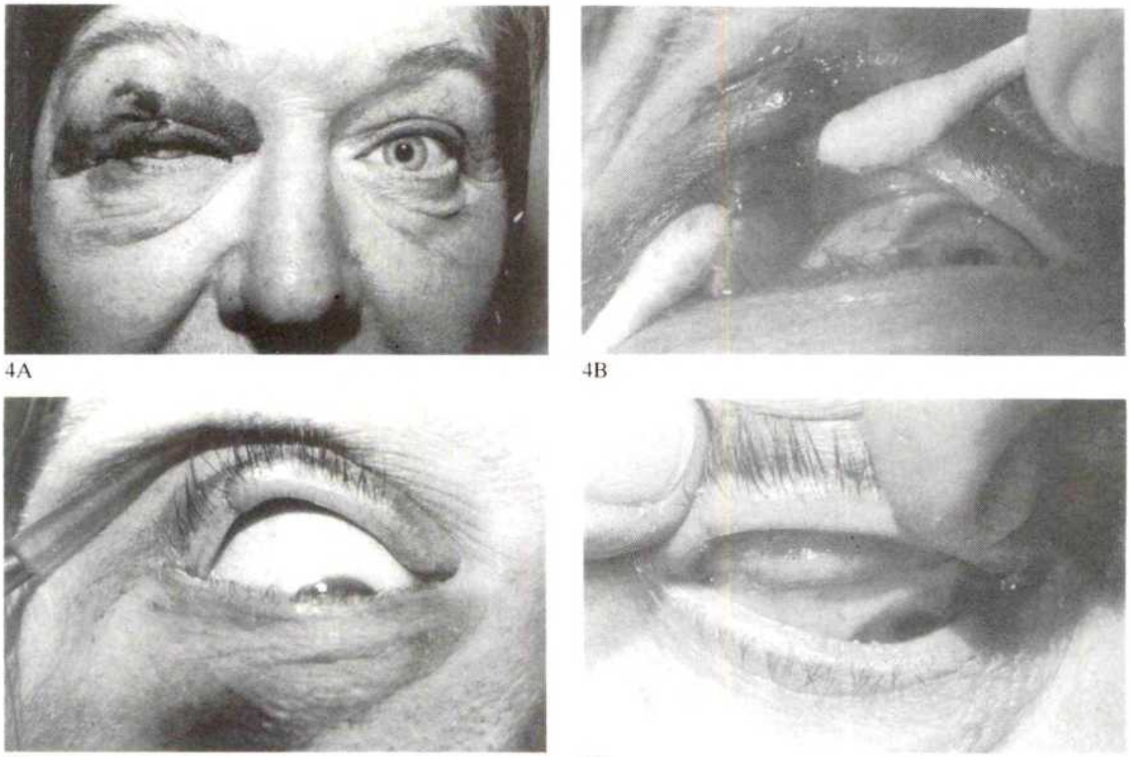
Results

HEALING PERIOD

This depended on the site and size of the excision. Small anterior lamellar excisions confined only to the skin healed within two weeks and regained normal appearance over the next two weeks. Deeper excisions involving the skin and orbicularis took slightly longer, with the largest deep juxtamarginal excision of 13×10 mm taking nearly four weeks to heal completely and regaining normal appearance over the next eight weeks. Among the FTMI excisions those at the inner canthus healed the quickest—the largest excision of 8×5 mm healed within three to four weeks. FTMI excisions of intercanthal areas of the upper eyelid took longer to fill the gap. The largest FTMI excision of 10×6 mm vertically in the central region (Fig. 2) healed in about eight weeks with continued cosmetic improvement over the ensuing 12 weeks. Even larger FTMI excisions of the intercanthal regions of the lower eyelid healed much more rapidly by comparison.[1]

FUNCTIONAL AND COSMETIC RESULTS

In all the 29 patients the functional results after solely spontaneous repair were excellent and fulfilled the requisite criteria for an optimal surgical repair as laid down by Mustardé[2]—a supple, mobile, resilient upper lid with a stable margin conforming to the contours of the globe. The mobility of the upper eyelid was normal in all 29 patients. None experienced feeling of tautness of the upper lid either when the lid was mobile or static. All had adequate eye closure. Of the four cases of trichiasis treated by FTMI excision one with recalcitrant trichiasis had recurrence of trichiasis in the 'newly formed' lid margin. During the process of spontaneous repair, and subsequently, none of the 29 patients developed or experienced exposure conjunctivitis or keratitis. No patient had sepsis, delayed or non-healing of the wound, epiphora, distortion of eyelid, symble-



4A 4B 4C 4D

Fig. 4 (A) *FTMI laceration with a glancing blow from a shovel. The resulting wound was ⊢ shaped, with the horizontal limb lacerating the skin and orbicularis lamella. To control bleeding at the apex of the skin wound, a single suture of 6=0 Dexon was inserted, the apex of the skin wound being sutured to cover the bleeding vessel. This was the sole surgery implemented.* (B) *The vertical limb of the wound had cut the entire height of the tarsal plate and extended 4 mm above it.* (C) *Appearance at 2 weeks.* (D) *Final result at 8 weeks.*

pharon, or ocular or palpebral discomfort. Similarly, no patient had ptosis or retraction of the eyelid.

Cosmetic results were excellent in 27 patients and acceptable in two: one patient with an asymmetrical FTMI excision developed a small, shallow, slanting notch of the lid margin (Fig. 3), without ocular or palpebral symptoms during the three years of observation. The second patient was a young girl who had sustained severe facial injuries in a motorcar accident. She had FTMI loss of about a quarter of the upper eyelid at inner canthus. Spontaneous repair of the upper eyelid had yielded very acceptable cosmesis, but she subsequently underwent further faciomaxillary, rhinoplastic, and oculoplastic surgery.

SUBJECTIVE RESPONSES OF THE PATIENTS

Twenty-eight of the 29 patients were treated as day cases, the young girl with facial injuries was the only one who was admitted to the hospital. They were happy to have been treated as day cases. The 26 patients who underwent surgical excision were particularly pleased with the short surgical procedure of excision and subsequent symptom-free convalescence. They were also happy with the ultimate cosmetic and functional results. The patients with eyelid lacerations were also pleased at not having to undergo immediate surgical repair.

HISTOLOGY

This was studied in 21 patients, as four had trichiasis, three had FTMI lacerations, and one had nearly 50 small sebaceous cysts on the upper eyelid. The entire horizontal extent of the eyelid and 5 mm in height was studded with these cysts. Instead of attempting to remove each cyst individually, we removed the entire skin lamella with a very satisfactory result. Of the 21 lesions submitted for histological examination, seven were reported as rodent ulcers, two were benign pigmented naevi, two benign acanthosis with hyperkeratosis, one benign pigmented papillary seborrhoeic keratosis, one cutaneous horn—a polypoid exophytic tumour ('classical solar keratosis that has undergone acute inflammation and abscess formation'), one squamous papilloma, one benign surface necrosis with mucinous degeneration of superficial dermis, and the remaining six anterior lamellar excisions showed benign solar keratosis.

Discussion

The sine qua non for successful surgical management of palpebral cancers is adequate excision. So far the traditional teaching of oculoplastic surgery has led us to believe that immediate surgical repair after such excisions is obligatory. This is exemplified by the exhortation of Fox and Beard[3] that a lesion in the centre of the eyelid with healthy lid margin on each side cannot be left to chance, and that (surgical) 'Repair is mandatory, and unless undertaken will end up in notching, cicatricial entropion, or ectropion or loss of the eyelid.' However, the previous study on the lower eyelid[1] has shown the potential of near normal functional and cosmetic results of solely spontaneous repair after FTMI excisions—even of the *central* region—of nearly half the horizontal extent and 5–6 mm in vertical extent of the lower eyelid. There have been no reports of spontaneous repair of the upper eyelids till now.

The current concepts and principles of surgical repair of the upper eyelid are lucidly explained by Mustardé,[4,5] Roper-Hall,[6] and Hatt.[7] By conventional criteria none of the 29 patients reported in this study would have been treated by spontaneous repair. All of them would have required to undergo surgical repair or reconstruction by such surgical procedures as direct suturing of skin, local skin flaps, split-thickness or full-thickness skin graft. Mustardé,[8] discussing moderate to extensive superficial tissue loss of eyelids, states that 'Where the defect is too large to be closed by direct approximation of the edges, despite rotation of nearby skin—or perhaps because this is not practicable, a full-thickness skin graft, comprising both dermis and epidermis will be required to replace the lost tissue.' Therefore the result after sole spontaneous repair is particularly impressive in Fig. 1, where an excision of 13×10 mm of the skin and orbicularis lamella was carried out. It is almost certain that the firmness of the underlying tarsal plate counteracted distortional forces during spontaneous repair. A similar excision of the lower eyelid, especially at the medial or lateral ends would almost certainly have produced cicatrical ectropion with spontaneous repair. For reconstruction of FTMI defects of the upper eyelid Mustardé's[4,5] principles based on multiples of a quarter are almost universally accepted and are as follows.

Direct multilayer suturing (three layers) is advocated for FTMI loss of up to a quarter of the upper eyelid. About five of the 15 patients in group 3 and all the three patients with traumatic FTMI lacerations in group 4 would have conventionally been treated by direct multilayer suturing. It is quite likely that in at least two patients in this study such direct suturing might have produced mechanical ptosis by levator tethering, about which Mustardé[9] in his Fig. 8-3 has given warning. Similarly, McCord and Wesley[10] also emphasize the importance of a correct method of a pentagonal FTMI excision, if notching or buckling of the eyelid by direct suturing is to be avoided. It is gratifying to report that none of these complications occurred with spontaneous repair, except in one patient (Fig. 3), in whom a shallow slanting notch has resulted, probably from a defective asymmetrical excision.

For FTMI defects of between a quarter and a half of the upper lid a lateral cantholysis is usually necessary to allow direct closure. About six patients in group 3 would have been so managed by convention. It is therefore obvious that in all the 29 patients spontaneous repair has obviated the need for primary surgical repair, and has yielded a mobile upper eyelid that conforms to the contours of the globe and has a permanently stable lid margin. None of the patients in this study had an FTMI defect larger than two-fifths of the horizontal extent of the upper lid. Therefore defects larger than these should have surgical reconstruction, at least until a future study of spontaneous repair of such larger defects can prove that acceptable results can be attained.

In dealing with the upper eyelid, most clinicians fear exposure keratopathy. It should be appreciated that, unless there are qualitative or quantitative abnormalities of the tear film, or abnormal neurotrophic influences, simple inability of eye closure, even in the absence of Bell's phenomenon, does not result in exposure keratopathy. This is substantiated by detailed and prolonged observation of cases of simple Bell's palsy or traumatic facial nerve palsy. Roper-Hall[11] advocating the management of severe blepharospasm by facial nerve avulsion, affirms that 'Despite this operation, corneal exposure during sleep has not been recorded to date.' Further reassurance of the absence of exposure keratopathy despite incomplete eye closure for several years is furnished by the normal corneal appearance and absence of evidence of past or present ocular irritation in the clinical pictures of congenital coloboma of upper eyelids.[12,13] Roper-Hall,[14] discussing congenital coloboma of eyelids states that 'it is astounding that the apparently unprotected cornea can appear normal for several years.' However, he also states that on careful biomicroscopy corneal changes may be observed.

As stated above, the response of these 29 patients to management with spontaneous repair has been very favourable. They have expressed relief, approval, and satisfaction with the near normal results obtained, enjoyed a trouble-free healing period, and appreciated the simplicity of the treatment. The present study shows that satisfactory results are obtainable by solely spontaneous repair of moderate sized juxtamarginal, extramarginal, and full-thickness margin-inclusive excision of upper eyelids. These results are as good as those obtained by spontaneous repair of FTMI excision of nearly half the lower eyelid as reported by this author previously.

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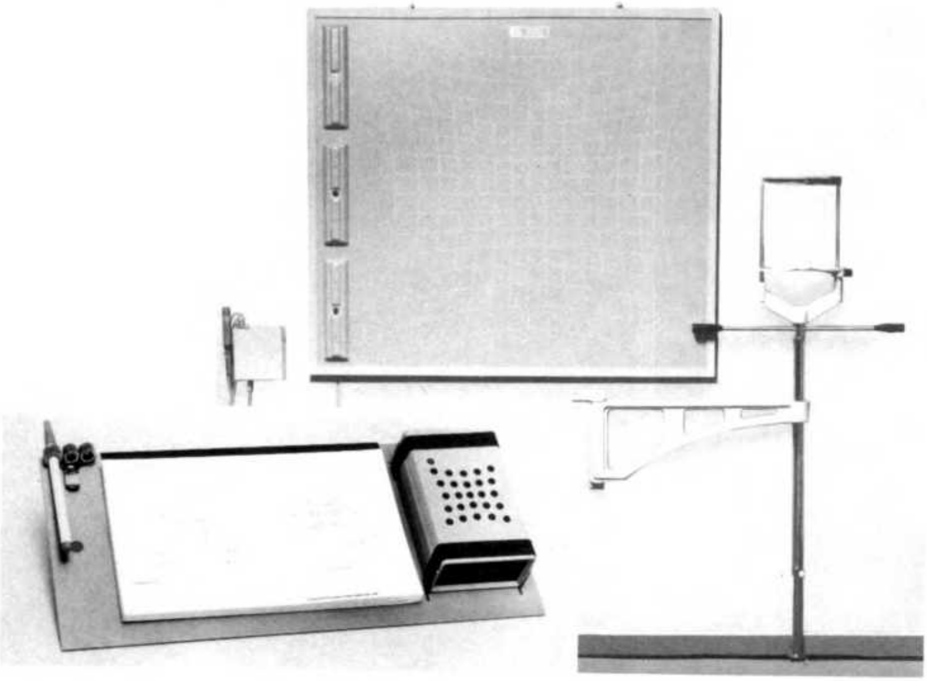

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Blepharochalasis*

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SUMMARY Blepharochalasis is an uncommon disorder distinguished by recurrent episodes of eyelid oedema in young patients. A hypertrophic form, manifested as fat herniation, and an atrophic form, manifested as fat atrophy, have been described. Ptosis with excellent levator function, laxity of the lateral canthal structures with rounding of the lateral canthal angle, nasal fat pad atrophy, and redundant eyelid skin develop after many episodes of eyelid swelling. Fine wrinkling, atrophy, and telangiectasias characterise the excess eyelid skin. We describe four cases of this syndrome in which external levator aponeurosis tuck, blepharoplasty, lateral canthoplasty, and dermis fat grafts were used to correct atrophic blepharochalasis after the syndrome had run its course.

Blepharochalasis is an uncommon disorder characterised by recurrent, non-painful, non-erythematous episodes of eyelid oedema. It must be distinguished from dermatochalasis, which is an involutional change of eyelids and is associated with loose, redundant skin.[1] Beer[2] was the first to describe this entity in 1807, and Fuchs[3] coined the term blepharochalasis in 1896. It has been divided into hypertrophic and atrophic forms.[4,5] In the hypertrophic form recurrent oedema results in orbital fat herniation through a weakened orbital septum. Most patients who have blepharochalasis present in an atrophic condition with atrophy of redundant eyelid skin and superior nasal fat pads. Most of these atrophic patients do not go through a hypertrophic phase.

Multiple attacks of eyelid oedema result in thinning, stretching, and atrophy of eyelid tissues. The eyelid skin becomes redundant, discoloured, and atrophic, appearing like wrinkled cigarette paper. The upper eyelids are more commonly affected, but the lower eyelids may also be involved. Laxity of the lateral canthal tendon results in rounding of the lateral canthal angle and blepharophimosis. Dehiscence and thinning of the levator aponeurosis results in blepharoptosis associated with excellent levator palpebrae superioris function.[6] Pseudo-epicanthal folds are formed by atrophy of the superior nasal fat pads. Numerous cases of blepharochalasis have been reported.[7-34] Our report describes four patients who had atrophic blepharochalasis that was treated surgically.

Case reports

CASE 1

A 27-year-old woman had numerous attacks of upper and lower eyelids oedema in the previous 12 years, each lasting 3 to 5 days. The last attack had been one year earlier. She was in excellent health and had no family history of eyelid oedema. She was allergic to many foods and animal dandruff. The serum C1 esterase inhibitor level was within normal limits.

4 mm of bilateral upper eyelid ptosis, high supratarsal eyelid creases, and excellent levator function were noted (Fig. 1). There was fine wrinkling and mild hyperpigmentation of redundant eyelid skin, with multiple fine telangiectatic subcutaneous vessels. Mild atrophy of the upper nasal fat pads and dehiscence of lateral canthal tendon was evident (Fig. 2, left). A blepharoplasty and external levator aponeurosis tuck by the anterior approach corrected

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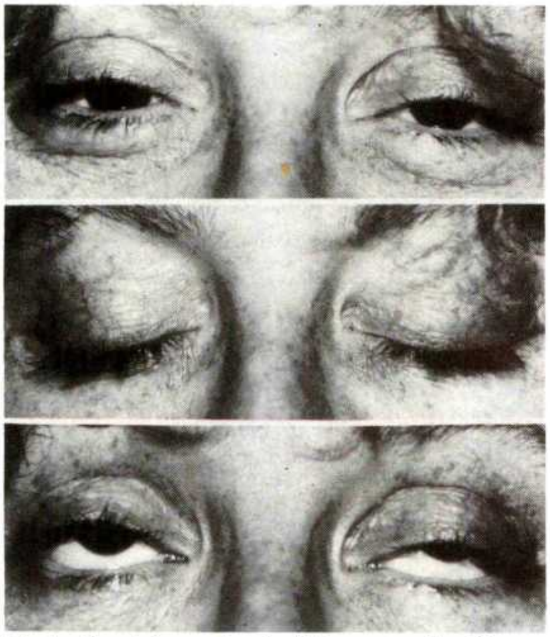

Fig. 1 *Case 1: 4 mm of ptosis, high supratarsal eyelid creases, and excellent levator function. 'Cigarette paper' thinning and telangiectasias of excess upper eyelid skin are evident. Note mild atrophy of nasal fat pad and pseudoepicanthal fold.*

the high lid crease, redundant skin, and blepharoptosis (Fig. 3). Lower eyelid blepharoplasty was combined with lateral horizontal eyelid shortening to attach the lateral border of the tarsus to the periorbita near Whitnall's tubercle. This procedure resulted in reformation of the lateral canthal angle (Fig. 2, right).

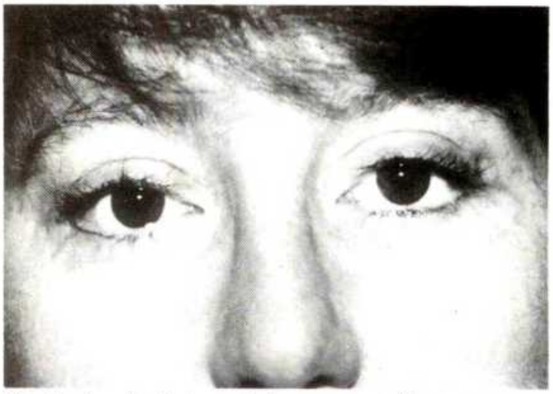

Fig. 3 *Case 1: photograph shows corrected features one year after four-lid blepharoplasty, upper eyelid levator aponeurosis tuck, and reformation of lateral canthal angle.*

CASE 2

A 28-year-old woman had bilateral acquired blepharoptosis of several years' duration (Fig. 4, left). She had recurrent attacks of upper eyelid oedema from ages 13 to 20, each lasting about three days. She had no allergies and her family history was negative. Test results with edrophonium chloride (Tensilon) and for serum Cl esterase inhibitor level were normal. Examination revealed bilateral ptosis of 3 mm, with excellent levator function and high supratarsal lid creases. The lid skin was atrophic, with prominent subcutaneous blood vessels. The atrophic nasal fat pads resulted in pseudoepicanthal folds (Fig. 4, right). Rounding of the lateral canthal angle was present. Other ocular and physical examinations gave normal results. An external levator aponeurosis tuck was combined with a blepharoplasty. The levator aponeurosis was markedly thin-

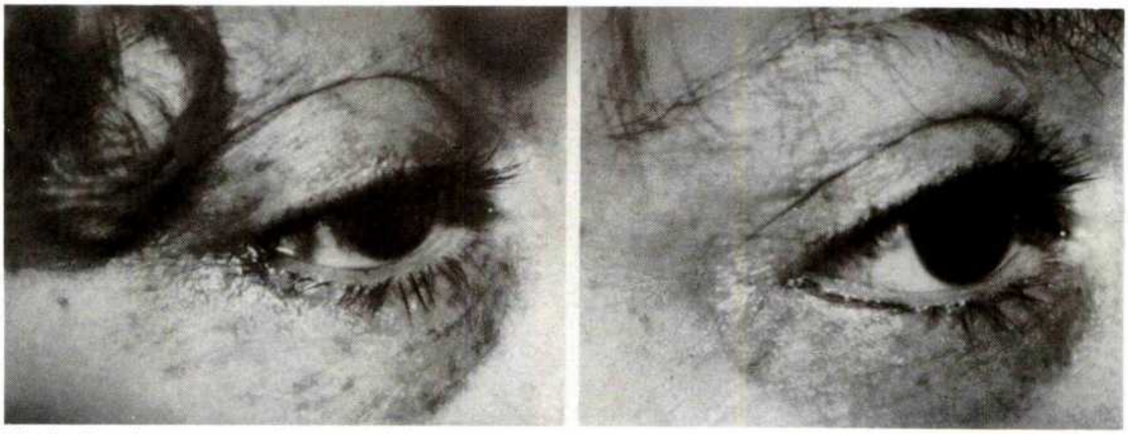

Fig. 2 *Case 1: preoperative photograph (left) shows rounding of the lateral canthal angle. Postoperative photograph (right) one year later shows reformation of lateral canthal angle.*

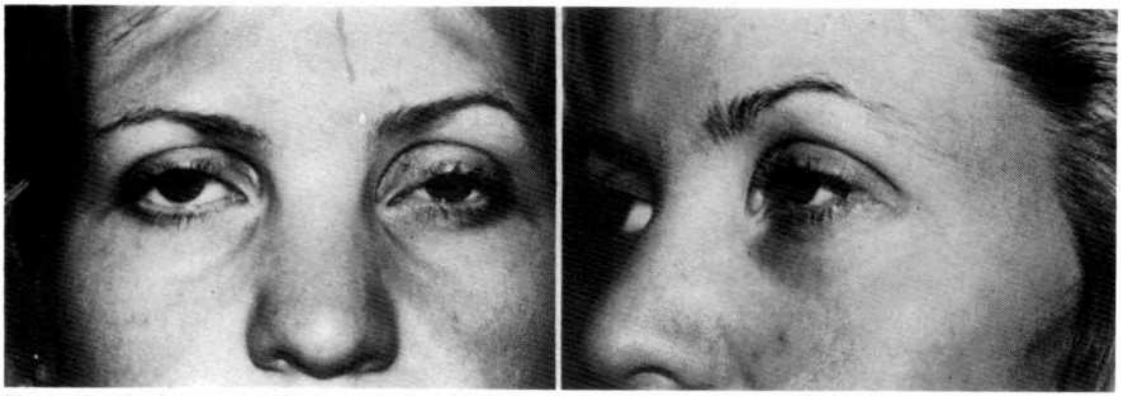

Fig. 4 *Case 2: photograph (left) shows ptosis and high supratarsal lid crease. Photograph (right) shows prominent nasal fat pad atrophy, pseudoepicanthal fold, and rounded lateral canthal angle.*

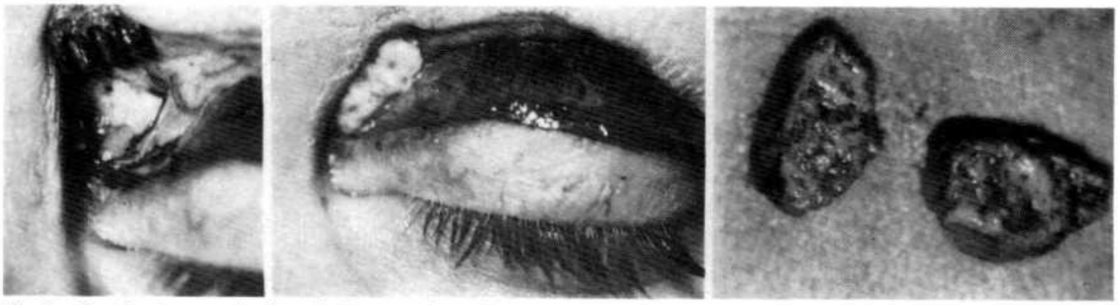

Fig. 5 *Case 2: photographs show (left) exposed atrophic superior nasal fat pad (centre), dermis fat graft fixed to perioribita of roof with double-armed 5-0 absorbable suture, and (right) dermis fat graft consisting mostly of dermis.*

ned (Fig. 5, centre). A dermis fat graft from the abdomen was placed in the superior nasal fat pocket and fixated to the periorbita of the orbital roof with a 5-0 absorbable suture (Fig. 5). A lateral canthoplasty reformed the lateral canthal angle. Four months after operation there was some residual nasal ptosis of the left upper eyelid, but an excellent cosmetic result was noted (Fig. 6).

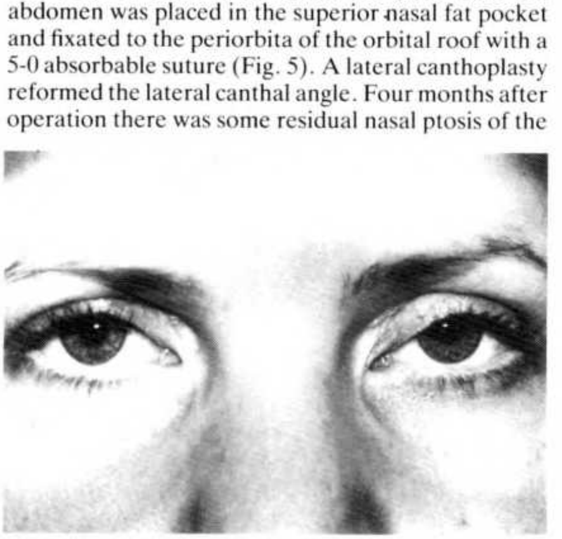

Fig. 6 *Case 2: photograph shows results one year after bilateral upper eyelid blepharoplasty, external levator aponeurosis tuck, dermis fat graft, and lateral canthoplasty.*

Surgical specimens from the first two cases gave identical histopathological findings. The epidermis was focally thin. Occasional vacuolated basal cells were noted. Melanin laden macrophages were present in the upper dermis. Vessels in the upper dermis were dilated and focally surrounded by a scant number of mononuclear cells. Elastic tissue stains showed a decreased amount of elastic tissue in the papillary and upper reticular dermis. Middle and deep dermal elastic fibres were fragmented and focally clumped.

CASE 3

A 20-year-old woman had had repeated attacks of upper and lower eyelid oedema since her early teens, with gradual onset of ptosis. She was allergic to pollen, moulds, and coconuts, and she had received injections for allergy in the past. There was no family history of eyelid oedema or ptosis. She was in excellent health, and the results of a physical examination were normal with the exception of her eyelids. Blepharoptosis, excellent levator function, and high

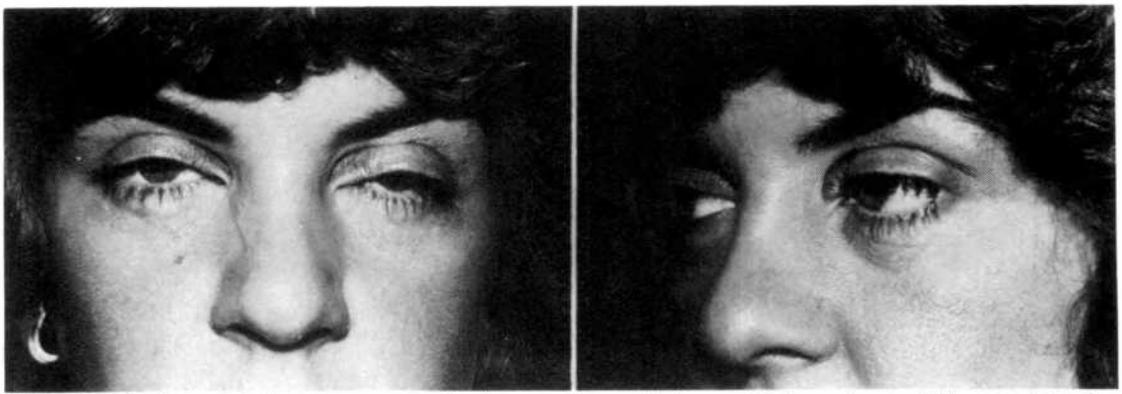

Fig. 7 *Case 3: photograph (left) show ptosis, redundant, atrophic eyelid skin, and high superior tarsal lid crease. Lateral view (right) shows nasal fat pad atrophy, psuedoepicanthal fold, and rounded lateral canthal angle.*

lid creases were noted (Fig. 7). Slight hyperpigmentation was present in the excess upper eyelid skin, which had fine wrinkling and telangiectasias. Atrophy of the superior nasal fat pads and pseudopepicanthal folds was prominent (Fig. 7). The lateral canthal tendon was dehisced. Four-lid blepharoplasty, external levator aponeurosis tuck, lateral canthoplasty, and dermal fat grafts to the superior nasal fat pockets corrected these abnormalities (Fig. 8).

CASE 4

A 13-year-old girl had multiple attacks of right and lower eyelid oedema for three years. In the spring she had trouble with allergies that were described as minor, and she was allergic to penicillin. There was no family history of similar problems. Her serum level of Cl esterase inhibitor was within normal limits. Right-sided wrinkling of the upper eyelid skin, upper eyelid ptosis, superior nasal fat pad atrophy, and lateral canthal tendon dehiscence were noted. These conditions were corrected by an upper eyelid blepharoplasty, external levator aponeurosis tuck, dermis fat graft, and lateral canthoplasty.

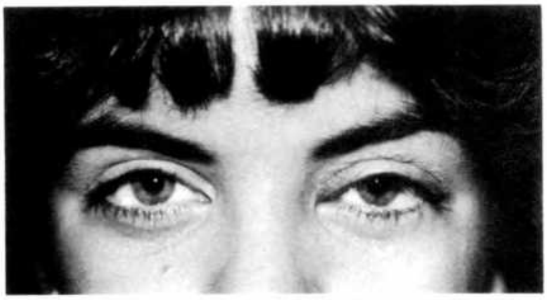

Fig. 8 *Case 3: photograph shows results six months after four-lid blepharoplasty, external levator aponeurosis tuck, dermis fat graft, and lateral canthoplasty.*

Discussion

Although our four cases occurred in women, blepharochalasis affects both sexes equally.[8] It is a disease of young people, who have symptoms that usually begin in the teens and become less frequent after a number of years. Blepharochalasis is not a hereditary disease, though Ranjini *et al.* speculated that autosomal recessive inheritance had occurred in one case.[9] The aetiology of the attacks of oedema is unknown. Patients who have angioneurotic oedema may develop signs of blepharochalasis,[25] but normal Cl esterase inhibitor levels ruled out this diagnosis in our cases.

Our histopathological findings correlated with the clinical picture and were similar to those in previous reports.[5 24 26] In response to recurrent inflammation and dilatation, blood vessels are increased in number and luminal size. Dermal elastic fibres are decreased in number and fragmented. This change occurred in part as the result of mechanical distortion of these fibres by repeated episodes of stretching resulting from oedema. The focally marked decrease of elastic fibres, even in the papillary dermis, suggests specific elastolysis by dermal inflammatory cells. The clinically observed hyperpigmentation of the lids was histopathologically represented by upper dermal melanin being present within macrophages. This hyperpigmentation is a non-specific finding observed after many inflammatory disorders of the skin.

Treatment for blepharochalasis is surgical. Since the frequency of oedema decreases with age, surgery should be deferred for at least one year from the previous attack of eyelid oedema. The acquired ptosis results from stretching or dehiscence of the levator aponeurosis. The retraction of the levator aponeurosis elevates the eyelid crease because of the fascial connections from the aponeurosis to the skin. An external approach to the levator aponeurosis tuck is recommended, because it offers better exposure of the abnormal anatomy and can be combined with an upper eyelid blepharoplasty through the same incision. By fixing the skin edges to the edge of the levator aponeurosis, normal symmetrical lid creases can be created. Local anaesthesia is preferred so that eyelid position can be adjusted readily at the time of surgery, decreasing the incidence of overcorrection that is common in the correction of acquired ptosis. In addition, through this incision a dermis-fat graft can be affixed to the periorbita in the superior nasal fat pocket with a double-armed 5-0 absorbable suture. More dermis than fat should be used; an additional 30% overcorrection usually gives an excellent cosmetic result. If there is redundancy of the lower eyelid skin, a lower eyelid blepharoplasty is performed in combination with a lateral canthoplasty. A lateral canthotomy, inferior cantholysis, and lateral full-thickness horizontal shortening of the eyelid may be performed if necessary. A 4-0 polypropylene suture is used to fixate the lateral edge of the tarsus to the periorbita near Whitnall's tubercle. This procedure will reform the lateral canthal angle.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government

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Testicular cancer presenting as a red swollen lid

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SUMMARY A case is reported in which a testicular cancer presented as a metastatic deposit in the eyelid. The histological appearances of both the metastasis and the subsequently detected primary were diagnostic of malignant teratoma trophoblastic (MTT). After comments on the testicular tumour, metastases occurring in the eye and adnexa are discussed.

A 19-year-old Army sapper was referred to the Ophthalmic Department at the Air Force Hospital in Germany from a nearby station medical centre with a five-day history of a painless red and swollen left upper lid. He had no other compaints, and there was no relevant past ocular or medical history. On examination the lateral aspect of the left upper lid showed a very vascular swelling. On lid eversion the subtarsal tissue was soft, friable, and bled to touch. There was no bulbar conjunctival injection, and the globe assessment, which included a fundal examination after mydriasis, was normal. Preauricular lymph nodes were not enlarged. The affected lid was infiltrated with 1% lignocaine, and piecemeal biopsies were taken from the subtarsal tissue and from just anterior to the lash line. Histological examination revealed metastatic tumour (see below).

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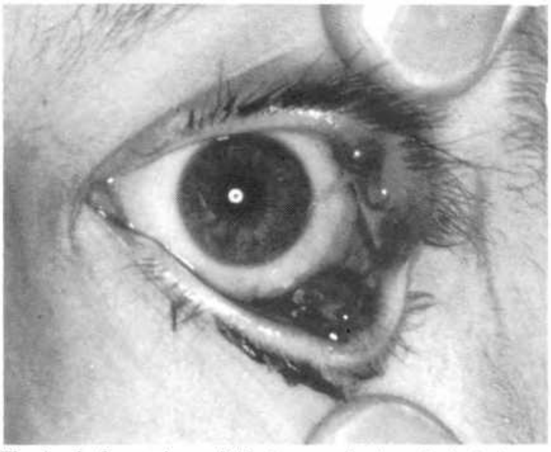

Fig. 1 *Left eye: the eyelid lesions on the day of admission.*

Four days later the patient was found to have spontaneous bleeding from his left eyelids. An increase in the size of the upper lid swelling had occurred, and a fresh haemorrhagic lesion in the lower fornix was noted (Fig. 1). A verbal report identifying the lid lesion as metastatic MTT was available, and the patient was admitted for further investigations immediately. He denied any lassitude, anorexia, or weight loss. He also denied any testicular abnormality, even on direct questioning. On examination he was a hirsute young man with no gynaecomastia or palpable lymphadenopathy. The

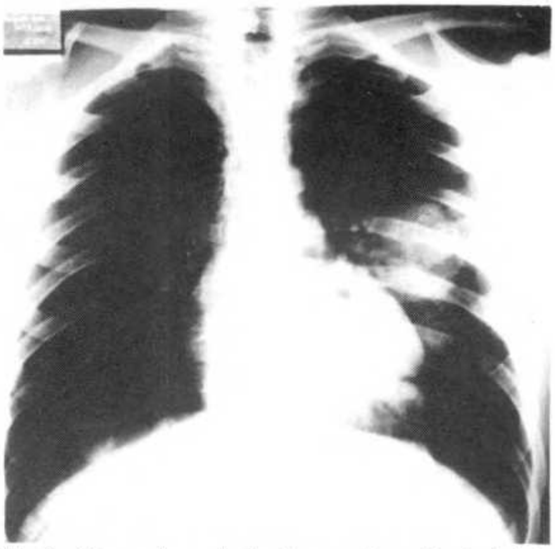

Fig. 2 *Chest radiograph showing round opacities in the left mid zone and right lower zone.*

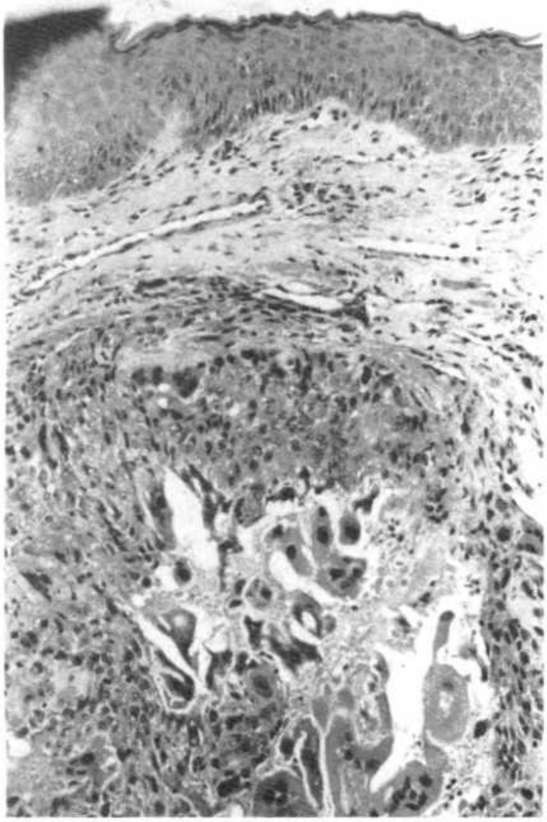

Fig. 3 *Section from an eyelid lesion showing metastatic MTT within the dermis. Multinucleate syncytial cells overlying cytotrophoblastic cells are clearly visible in relation to a blood filled space. The epidermis is seen in the upper part of the figure. H and E, ×110.*

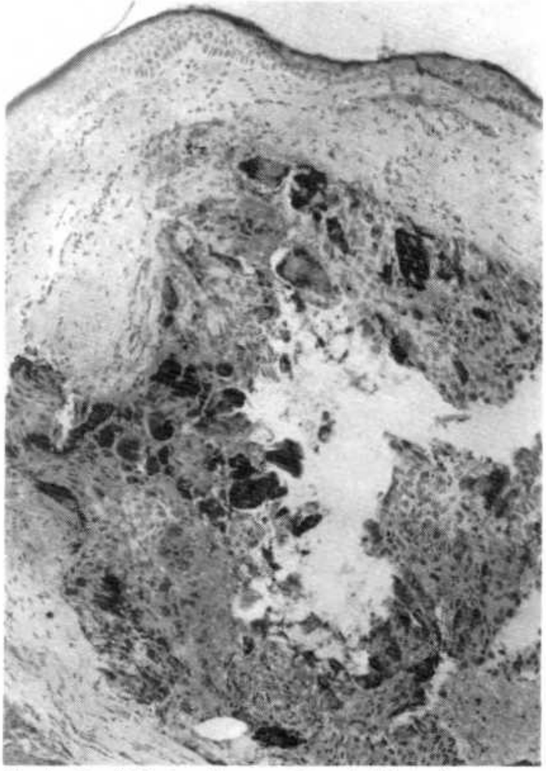

Fig. 4 *Eyelid lesion: the syncytiotrophoblasts show strong immunoreactivity with antibody directed against HCG. Immunoperoxidase, ×67.*

only abnormality on clinical examination was an obviously enlarged, nodular, non-tender, left testicle. Laboratory investigation revealed a haemoglobin concentration of 7·8 g/dl, and his chest radiography showed multiple round opacities in both lung fields (Fig. 2). An urgent orchidectomy was performed in Germany and histological examination confirmed the testis as the primary site of the MTT. Four days postoperatively he returned to the United Kingdom for further treatment in an oncological unit.

HISTOPATHOLOGICAL FINDINGS

The metastatic tumour in the eyelid was located in the dermis and composed of trophoblastic tissue surrounding blood spaces (Fig. 3). Immunohistochemical stains[1] showed the malignant cells to be strongly immunoreactive with antibody directed against human chorionic gonadotrophin (Fig. 4) and cytokeratin, but negative for α-fetoprotein and S100 protein.

The testicular lesion was composed of extensive areas of necrosis and haemorrhage within which tumour tissue was sparsely distributed. Syncytiotrophoblastic and cytotrophoblastic elements were clearly visible in relation to vascular spaces (Fig. 5). Also present were areas of organoid differentiation, which included cysts lined by squamous epithelium and bland cartilage, and partially differentiated areas. No yolk sac components were identified.

Discussion

Testicular tumours are almost invariably primary and malignant, presenting most commonly between the ages of 20 and 40.[2] Approximately 65% of patients present with a painless swelling, 20% complain of pain with or without swelling, and 10% of tumours are asymptomatic and detected on routine clinical examination. In less than 5% of cases does the patient present because of metastases. Initially metastases tend to occur in the para-aortic nodes and lungs; pulmonary spread may be detected by routine

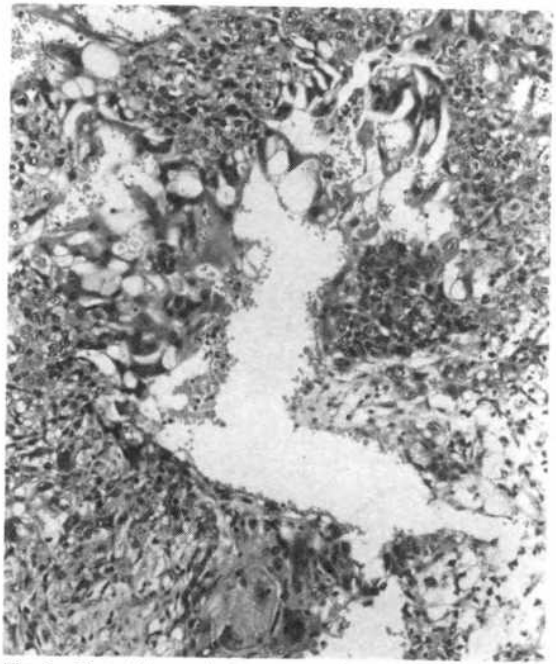

Fig. 5 *Part of the testicular tumour showing similar morphology to that seen in the eyelid lesion. H and E, ×93.*

chest *x*-rays. A dermal metastasis is an unusual presentation for a testicular tumour. In this case the primary could have been detected earlier, but the patient failed to present in spite of marked painless swelling of one testicle.

Teratomas account for approximately 30% of testicular tumours, and about 4% of these are MTT, also known as testicular choriocarcinoma. The histology of teratomas varies from well differentiated lesions, commoner in childhood, to the more malignant lesions graded intermediate or undifferentiated. According to the British Testicular Tumour Panel the following criteria are required for the histological diagnosis of MTT:[3] the presence of recognisable syncytiotrophoblastic and cytotrophoblastic elements, and their arrangement in a papillary pattern. Both the eyelid lesion and the testicular tumour satisfy these criteria. The appearances closely resemble those seen in gestational choriocarcinoma in the female.

Most metastases encountered by the ophthalmologist are intraocular or orbital; metastatic deposits in the eyelid are rare. Only 15 cases of secondary tumour in the eyelid were seen at the Mayo Clinic between 1922 and 1969.[4] The lesions in this series tended to occur as a manifestation of generalised carcinomatosis, and in only two cases (both of which were adenocarcinoma of the stomach) were the eyelid lesions the presenting complaint. Deposits in the eyelid from primaries in the breast, skin (malignant melanoma), and lung have been reported in particular, but other primary sites include colon, stomach, prostate, thyroid, kidney, and cervix.[4,5]

Metastatic lesions of the eyelid are said to take one of three forms.[6] Firstly, solid subcutaneous nodules occur which may be mistaken for chalazia. Secondly, an ulcerating lid lesion may occur which may mimic a basal cell carcinoma clinically. Thirdly, a diffuse swelling may result with non-tender thickening and induration of the eyelid. This case was unusual in that the trophoblastic nature of the deposit caused bleeding on eversion of the lid. With metastatic tumours of the eyelid the vascular reaction may suggest an inflammatory lesion rather than a neoplasm, and in this case the initial referring medical officer had made a provisional diagnosis of an inflammatory lesion.

In contrast to eyelid metastases, metastases to the eye and orbit are well described in the literature. The majority are blood borne following pulmonary involvement. In a review of 220 cases of carcinoma metastatic to the eye or orbit,[7] which comprised all cases on file in the Registry of Ophthalmic Pathology at the Armed Forces Institute of Pathology, Washington, DC, 28 patients had orbital metastases and in 17 cases symptoms of the orbital lesions preceded detection of a primary tumour elsewhere in the body. One patient in this series was a 20-year-old male with intraorbital metastasis from a testicular choriocarcinoma.

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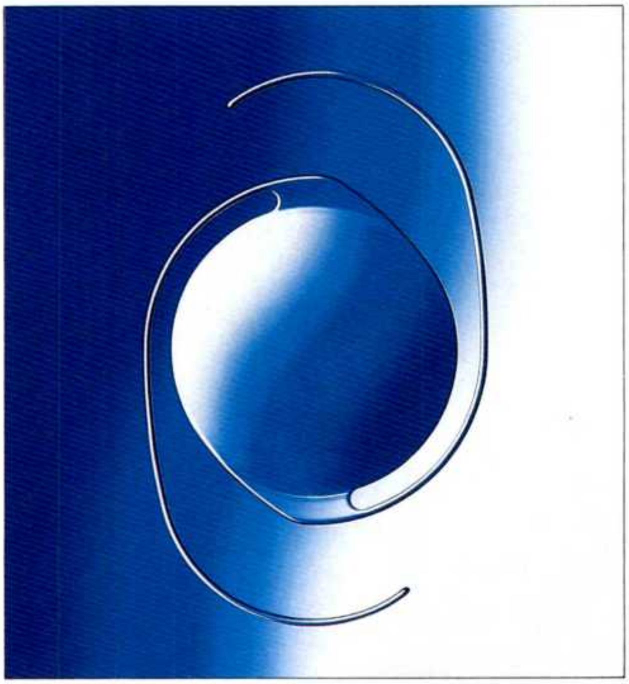

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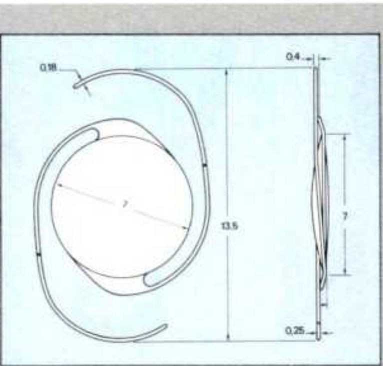

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Bilateral orbital cavernous haemangiomas

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SUMMARY Simultaneous bilateral orbital lesions are rare. The differential diagnosis includes orbital pseudotumour, metastasis, leukaemia, lymphoma, Wegener's granulomatosis, and neurofibromatosis. We report what we believe to be the first case of bilateral orbital cavernous haemangiomas.

Cavernous haemangioma is the most common primary adult benign orbital tumour.[1,2] It usually presents in middle aged adult females with slow, painless onset of unilateral proptosis. Multiple unilateral cavernous haemangiomas have been reported.[2] Cavernous haemangiomas have been diagnosed several years apart, as growing during pregnancy, or in association with haemangiomas elsewhere.[3-4] To our knowledge this is the first reported case of bilateral orbital cavernous haemangiomas.

Case report

A 48-year-old white male developed bilateral swelling of the eyes. Four to five years previously he noted a slowly increasing prominence of both eyes, the right somewhat greater than the left. Two years previously he observed that his eyelashes touched the inner surface of his spectacle lenses and four months prior to referral began noting bilateral epiphora. No redness, pain, diplopia, decreased vision, or headache was reported. The past medical history and results of systemic examination were negative.

The best corrected visual acuity was 20/25 OD and 20/30 OS. The pupils were 3 mm in size, reactive to light, and were without an afferent defect. Examination of ocular motility revealed mild limitations in all fields of gaze without diplopia. Colour vision was normal. Hertel exophthalmometry at a base of 96 measured 23 mm OD and 20 mm OS. External examination revealed 2 mm of inferior scleral show on the right and 1·5 mm on the left. Prominent insertions of the horizontal rectus muscles were noted in both eyes. No orbital mass was palpable. A subtle lid lag was present. Slit-lamp biomicroscopy, applanation tonometry, automated visual fields, and fundus examination were normal.

1·5 mm axial computed tomography views of both orbits, with coronal reconstructions, were obtained with and without contrast Bilateral, moderately enhancing, homogeneous, smooth-contoured masses were seen. The right lesion was ovoid, displaced the globe anteriorly, displaced the optic nerve nasally, and showed mild bony orbital wall contour changes. The mass was approximately 30×15×12 mm. Because of the unusual feature of bilateral, simultaneous orbital masses the patient was referred to the UCSF Ocular Oncology Unit for examination and therapy.

Initial examination of the patient gave findings similar to those already presented. A magnetic resonance imaging (MRI) scan was performed on a 1·5 Tesla superconducting magnet (General Electric) with orbital surface coils (General Electric). Sections of 3 mm at 4·5 mm intervals in transverse, sagittal, and coronal planes were obtained. Spin-echo technique with routine T1-weighted examination was performed with a repetition time (TR) of 600 ms and an echo time (TE) of 20 ms. The Ts-weighted examination had a TR of 2000 ms and a TE of 70 ms. This scan revealed similar information as was gathered on CT. A bilobed, lateral, intraconal, homogeneous mass was localised in the right orbit. The single tumour in the left orbit was both intraconal and extraconal at the inferior temporal aspect of the posterior orbit. The lesions were isointense with brain and sharply contrasted against orbital fat on both T_1 and T_2 weighted images (Figs. 1A, B).

Our clinical and radiological impression was of cavernous haemangioma of the orbit, but owing to

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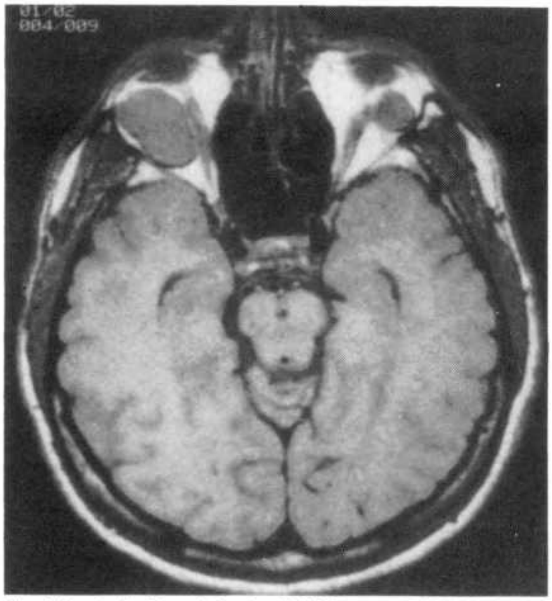

Fig. 1A *Left: T_1-weighted axial MR image (TR 600:TE 25) of orbital cavernous haemangiomas.*

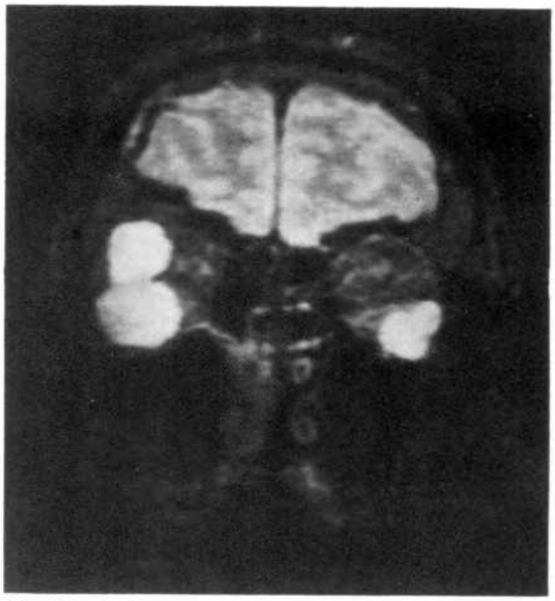

Fig. 1B *Right: T_2-weighted coronal MR image (TR 2000: TE 70) outlining bilateral orbital cavernous haemangiomas.*

the bilaterality doubt remained. At right orbitotomy a large, bilobed, smooth, encapsulated tumour was removed intact without complication (Fig. 2). Histologically this proved to be a cavernous haemangioma. Ocular movements and proptosis returned to normal postoperatively. Owing to a paucity of symptoms OS, no operation has been performed.

Discussion

Bilateral proptosis is most commonly caused by endocrine ophthalmopathy. Other less common causes include pseudotumour, Wegener's granulomatosis, other vasculitides, metastases, leukaemia, lymphoma, cavernous sinus thrombosis, and neuro-

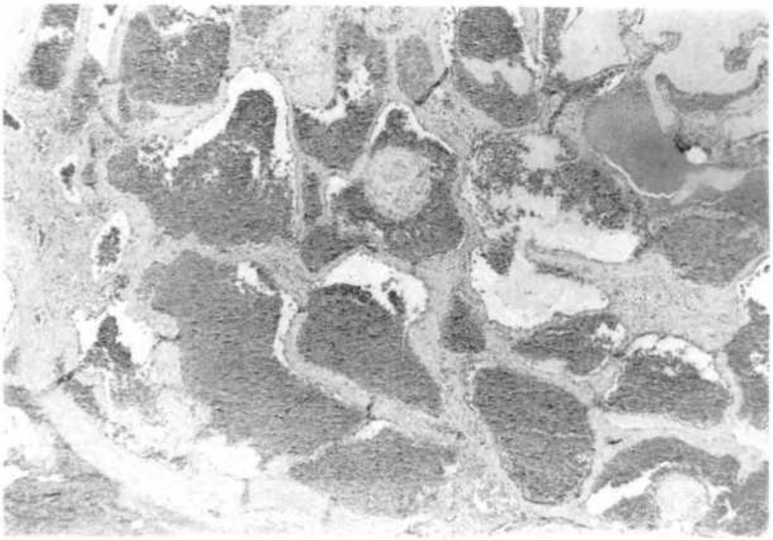

Fig. 2 *Histology of specimen removed from the right orbit. Large blood filled spaces separated by fibrous septa are typical of orbital cavernous haemangioma. H and E ×6.*

fibromatosis.[1,7-10] Computed tomography and magnetic resonance imaging will usually distinguish diffuse from solitary orbital processes. The typical CT findings of cavernous haemangioma of the orbit are its homogeneous, ovoid, smooth-margined appearance. Usually it is intraconal, shows minimal orbital bone expansion, enhances with contrast, and spares the orbital apex.[11] These features allow differentiation from diffuse orbital processes. However, more localised entities such as neurofibroma, neurolemmoma, benign mesenchymal tumour, or haemangiopericytoma may show a well circumscribed, oval mass.[11,12] In our case the diagnosis was suspected but not confirmed until surgical resection, because no previous cases of bilateral cavernous haemangioma of the orbit have been reported.

The pathogenesis of orbital cavernous haemangioma is not clear. Probably they arise as acquired lesions due to localised, progressively ectatic, capillary-type proliferation resulting in large vascular spaces.[2] Witschel and Font, in their study of haemangioma of the choroid, proposed that localised haemodynamic disturbances may be a nidus to initiate the development of these lesions.[13] Hood maintained that growth is not due to proliferation of vascular elements but rather to canalisation and blood flow into pre-existing vascular malformations secondary to changing systemic haemodynamics.[14] None of these theories suggest a rationale other than random chance to explain the bilaterality of the cavernous haemangiomas observed in our case.

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Detection and quantification of S-100 protein in ocular tissues and fluids from patients with intraocular melanoma

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SUMMARY S-100 protein is a 21 000 dalton acidic calcium-binding protein present in ocular melanomas and some normal ocular tissues. Ocular fluids and extracts of ocular tumours were examined by a sensitive radioimmunoassay that could detect less than 5 ng of S-100 protein in minute volumes of fluid. Three ocular melanoma biopsy specimens had S-100 protein at levels between 25 and 1300 ng/ml, comparable to that found in a cutaneous melanoma biopsy specimen (1000 ng/ml). *(SI conversion: ng/ml=μg/l.)* Six melanoma culture lines had 1000 to 125 000 ng/ml. Four lymphoblastoid cultures had less than 2 ng/ml, and three colon carcinoma cultures had 180 ng/ml. Subretinal fluid from 23 melanoma-containing eyes had 10 to 76 800 ng/ml. Lesser amounts were found in eyes with small, anteriorly located, lightly pigmented tumours. Vitreous from 3 melanoma-containing eyes had 10 000 to 11 000 ng/ml. Vitreous obtained from three eyes during tractional retinal detachment repair had 500 to 1600 ng/ml, and vitreous obtained at necropsy from six normal eyes had 2 to 120 ng/ml. Aqueous from six melanoma-containing eyes had 10 to 30 ng/ml, levels not significantly different from those observed in three normal eyes (80–120 ng/ml). This approach provides new insight into the interaction of ocular tumours and adjacent ocular fluids and may, with more specific tumour markers, have diagnostic applications.

Early and accurate diagnosis offer cancer patients the best chance of survival. In ocular melanoma, ophthalmoscopy and supplementary techniques such as fluorescein angiography, ultrasonography, or ^{32}P uptake permit an accurate diagnosis to be made in most patients.[1] In occasional patients, however, conditions such as a rhegmatogenous retinal detachment with associated subretinal blood, non-neoplastic exudative detachment, or tumours metastatic to the choroid may be difficult to differentiate from a primary intraocular melanoma.

To differentiate patients with intraocular melanoma from those with non-melanomatous tumours or conditions simulating ocular tumours attempts have been made to find evidence of tumour-related immune reactivity.[2,3] Although immunological reactions are of some value in separating groups of ocular melanoma patients from those without melanoma, they are insufficiently discriminatory when applied to the individual patient.

As a possible alternative diagnostic approach the detection of a melanoma product or melanoma cell constituent in the vitreous or aqueous fluids was considered. S-100 protein is a marker that is universally present in abundant quantities in cutaneous malignant melanoma, though not specific for this tumour The authors have recently demonstrated the presence of S-100 protein in ocular melanomas.[4] S-100 protein was therefore sought in fluids from eyes with intraocular melanoma or other, non-

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melanomatous disease processes. A study of S-100 protein distribution within the eye could also provide valuable information on the basic biology of intraocular tumours and the extent to which tumour-derived molecules permeate the eye. The availability of a sensitive radioimmunoassay made it possible to detect nanogram quantities of S-100 protein with great precision in minute samples

Materials and methods

The quantity of S-100 protein was determined in tissues from three ocular melanomas, one cutaneous melanoma, one ocular glioma, and normal brain and sclera Twenty-three subretinal fluid samples, 22 vitreous samples, and nine aqueous humour samples were also examined. Fluids from patients who had undergone cataract extraction and from corneal donors served as controls Tumour tissues and ocular fluids were contributed by members of the Tennent Institute of Ophthalmology, Glasgow, Scotland, and the Jules Stein Eye Institute, Los Angeles, CA. Melanoma tissue and fluids were obtained during tumour resection (Tennent Institute) or immediately after enucleation. The Tennent Institute samples were transported to UCLA in a frozen state, and all samples were stored at −70°C. All diagnoses were established clinically and confirmed histologically where appropriate. Tissue culture cell lines (six melanomas, four lymphoblastoid, and three colon carcinomas) were obtained from the tissue culture collection, Division of Surgical Oncology, UCLA. All samples were coded, and diagnoses were not available to individuals performing radioimmunoassays until the S-100 protein content had been recorded.

RADIOIMMUNOASSAY FOR S-100 PROTEIN

Tissue specimens were weighed to determine 50% weight/volume, minced finely with scissors, and resuspended in lysis buffer (0·5% NP40, 150 mM NaCl, 10 mM Na_2, HPO_4, pH 7·4) for 30 minutes Tissue debris was removed by pelleting for 5 minutes at 13 000 *g* in microfuge tubes. Samples of eye fluids and pelleted tissue culture lines were solubilised by mixing with an equal volume of lysis buffer at 4°C for 30 minutes.

The radioimmunoassay was performed on dilutions of each solubilised test sample in duplicate microfuge tubes containing 100 µl RIA buffer (150 mM NaCl, 0·5 mM $MgSO_4$, 0·15 mM $CaCl_2$, 0·1% bovine serum albumin, and 10 mM trometamol (TRIS), pH 7·4). Control samples containing serial doubling dilutions of bovine brain S-100 protein (range 1–500 ng/ml) were included in separate duplicate tubes for each assay. Radiotracer at 5×10^4 cpm/50 µl (10 ng ^{125}I-S-100 protein, 5×10^6 cpm/µg) was added to each tube, followed by 50 µl of rabbit anti-S-100 protein serum (1·64 000 final dilution). After incubation at 4:C for 18 hours, immune complexes were isolated by adding 25 µl of 10% w/v prewashed *Straphylococcus aureus* (Pansorbin, Calbiochem) for 1 hour at 4°C. Bound radioactivity was determined in a gamma spectrometer after repeated washing and pelleting of bacteria at 13 000 *g* in a microfuge. S-100 protein antigen concentration in test samples was calculated from the midpoint of the standard S-100 protein competitive binding curve included with each assay. Maximum S-100 protein radiotracer binding of 10^4 cpm and minimum binding of 300 cpm allowed detection of less than 5 ng of S-100 proteon. *(SI conversion: ng/ml=µg/l).*

Results

Table 1 lists the S-100 protein content of intraocular tumours and normal tissues. Two of three primary intraocular melanomas contained substantial S-100 protein (1300 and 1200 ng/ml of tumour extract), while a third contained little S-100 protein (25 ng/ml). There was no apparent correlation between S-100 protein content and tumour size or cytology. The tumour that contained little S-100 protein was the most heavily pigmented. Substantial levels of S-100 protein were present in extracts of a biopsy sample of cutaneous melanoma that had metastasised to the inguinal lymph nodes (1000 ng/ml), a low-grade retinal peripapillary astrocytoma of mixed morphological pattern (480 ng/ml), and normal brain tissue obtained at necropsy (2500 ng/ml). Normal sclera contained little S-100 protein (<25 ng/ml of extract). *(SI conversion: ng/ml=µg/l.)*

Table 2 lists the S-100 protein content of a number of tissue culture cell lines. Extracts of six melanoma derived cell lines contained substantial but varied

Table 1 *S-100 protein content of tumour biopsies and normal tissues*

Tumour classification	*S-100 protein (ng/ml)*	*Ocular melanoma tumour characteristics*			
		Site	*Volume (mm^3)*	*Cytology*	*Pigment*
Ocular melanoma case 1	1300	Choroid	1515	Mixed	Light
Ocular melanoma case 2	1200	Choroid	840	Spindle	Light
Ocular melanoma case 3	25	Choroid	1870	Mixed	Heavy
Cutaneous melanoma*	1000				
Ocular glioma	480				
Normal brain	2500				
Normal sclera	<25				

*Metastatic deposit in inguinal lymph node
SI conversion ng/ml=µg/l

Table 2 *S-100 protein content of cultured cell lines*

Cell line	*Cell type*	*S-100 protein (ng/ml)*	*Melanin content*
M20*	Melanoma	125 000	Light
M21	Melanoma	80 000	Light
M1q	Melanoma	80 000	Light
M32	Melanoma	25 600	Light
M926	Melanoma	12 800	Light
M12	Melanoma	1 000	Heavy
L20*	Lymphoblastoid	<2	None
LDOn	Lymphoblastoid	<2	None
L14	Lymphoblastoid	<2	None
PL3	Lymphoblastoid	<2	None
DONCA	Colon carcinoma	180	None
HT29	Colon carcinoma	180	None
SW116	Colon carcinoma	180	None

*M20 and L20 are paired cultures derived from the same patient.
SI conversion ng/ml=μg/l.

amounts of S-100 protein (1000–125 000 ng/ml). Four lymphoblastoid cell lines, produced by Epstein-Barr virus transformation of peripheral blood lymphocytes, contained virtually no S-100 protein. Among them was a lymphoblastoid cell line (L20) that was autologous to a melanoma cell line (M20) that contained 125 000 ng/ml of S-100 protein. Three colon cancer lines had relatively small amounts of S-100 protein (180 ng/ml).

Table 3 *S-100 protein content of subretinal fluid from patients with ocular melanoma*

Patient	*S-100 protein (ng/ml)*	*Ocular melanoma tumour characteristics*			
		Site	*Volume (mm³)*	*Cytology*	*Pigmentation*
1	76 800	Choroid	1632	Mixed	Light
2	64 000	Choroid	2475	Mixed	Moderate
3	2200	Angle/CB*	972	Mixed	Moderate
4	160	Choroid (anterior)	540	Mixed/ inflammatory	Light
5	80	CB	470	Mixed/ inflammatory	Heavy
6	32 000	Choroid	3168	Mixed	Heavy
7	14 000	CB/choroid	2720	Mixed	Light
8	32 000	Choroid	258	Spindle	Light
9	18 000	Choroid	117	Spindle	Light
10	12 500	Choroid	450	Spindle	Light
11	12 000	CB/choroid	1512	Spindle	Light
12	2176	CB/choroid	960	Mixed	Patchy/heavy
13	896	Choroid	2025	Mixed	Light
14	<10	CB	243	Mixed	Heavy
15	15 000	Choroid	840	Mixed	Moderate
16	2048	Choroid	594	Spindle	Moderate
17	640	Choroid	960	Spindle	Heavy
18	768	Choroid	2535	Mixed	Patchy
19	50	Choroid (anterior)	1188	Mixed	Patchy
20	16	Choroid	2880	Mixed	Very heavy
21	8192	Choroid	2016	Spindle	Light
22	8192	Choroid	3042	Mixed	Moderate
23	3000	Choroid	1904	Mixed	Moderate

*CB=ciliary body
SI conversion: ng/ml=μg/l

Table 3 lists S-100 protein content of subretinal fluid from eyes containing melanomas. The S-100 protein content of fluids varied from negligible (<10 ng/ml) to very high (76 800 ng/ml). Subretinal fluids that contained substantial (>1000 ng/ml) S-100 protein were usually from patients with light to moderately pigmented tumours (13 of 15). Many were composed primarily of spindle type cells (6 of 15). By contrast, subretinal fluids that contained little S-100 protein came from patients with tumours of mixed cytology (7 of 8) and tumours with substantial pigmentation (6 of 8). Four of 8 tumours that contained <1000 ng/ml S-100 protein were located in the anterior part of the eye, including two ciliary body tumours. By contrast only 4 of 15 tumours located more posteriorly were low in S-100 protein.

Table 4 lists S-100 protein content of vitreous from eyes with tumours and from normal patients. In vitreous samples from eyes containing melanomas a range of S-100 protein content from less than 10 ng/ml to 11 000 ng/ml was encountered. Vitreous fluids containing abundant (>1000 ng/ml) S-100 protein were from patients with moderate sized to large tumours (262–1512 mm³) that were usually lightly pigmented (4 of 5) and choroidal in origin. Low S-100 protein content was found in vitreous from patients with both large and small tumours. Three of 8 were substantially pigmented. Most were of mixed cellularity (5 of 8). Two were of iris or ciliary body origin.

Vitreous from one melanoma patient (no. 13) was obtained during vitrectomy three months after removal of the tumour. It contained little S-100 protein (16 ng/nl). Vitreous fluids from patients with rhegmatogenous retinal detachment were found to have detectable levels of S-100 protein (mean, 533 ng/ml), higher than that detected in normal eyes (mean, 64 ng/ml).

Table 5 lists S-100 protein levels in aqueous humour obtained from eyes with melanoma and from patients without tumours. All contained detectable but very low levels of protein.

Discussion

S-100 protein, first extracted from bovine brain by Moore[5] and named for its solubility in saturated ammonium sulphate at neutral pH, is a thermolabile, acidic, calcium-binding protein with a molecular weight of 21 000 daltons.[6-8] The molecule is a dimer composed of two very similar subunits a and b, each with a molecular weight of 10 500. Three dimeric forms exist: S-100^{ao} (aa), S-100^{a} (ab), and S-100^{b} (bb).[8] Amino acid sequencing has shown similarities

Table 4 *S-100 protein content of vitreous*

Patient	*Disorder*	*S-100 protein (ng/ml)*	*Ocular melanoma tumour characteristics*			
			Site	*Volume (mm^3)*	*Cytology*	*Pigmentation*
1	Melanoma	11 000	Choroid	450	Spindle	Light
2	Melanoma	3400	Choroid	1400	Mixed	Heavy
3	Melanoma	8500	Choroid	1512	Spindle	Light
4	Melanoma	2000	Choroid	262	Spindle	Light
5	Melanoma	1024	Choroid	720	Mixed	Light
6	Melanoma	240	Iris	144	Spindle	Light
7	Melanoma	160	Choroid	720	Mixed	Light
8	Melanoma	<10	Choroid	840	Mixed	Moderate
9	Melanoma	<10	Iris/CB*	60	Mixed	Light
10	Melanoma	40	Choroid	1515	Mixed	Moderate
11	Melanoma	480	Choroid	840	Spindle	Light
12	Melanoma	<10	Choroid	1870	Mixed	Heavy
13†	Melanoma	16	Choroid	1372	Spindle	Light
14	RD‡	500				
15	RD	600				
16	RD	500				
17	Normal	90				
18	Normal	80				
19	Normal	60				
20	Normal	30				
21	Normal	<2				
22	Normal	120				

*CB=ciliary body
†Specimen obtained at vitrectomy three months after local removal of tumour.
‡RD=retinal detachment
SI conversion ng/ml=µg/l

between S-100 protein and other calcium-binding proteins such as calmodulin, troponin-C, and parvalbumin.[8] Sequencing also reveals a close similarity of S-100 protein in many different species, indicating a striking conservation of S-100 protein during evolution.[9] It is present in the cytoplasm and nucleoplasm of cells and may also be present in a membrane-bound form.

Following its identification in brain, S-100 protein was identified in glial cells,[10] Schwann cells and satellite cells,[11] melanocytes,[12] and cultured melanocyte-derived cells,[13] satellite cells of the adenohypophysis,[14] satellite cells of the adrenal medulla,[15] sustentacular cells of the carotid body,[16] and interstitial cells of the pineal gland.[17] The fact that these cell types are all either neural or neural crest derivatives led to the hypothesis that S-100 protein might be a marker for cells of neural crest origin. It is now clear, however, that S-100 protein is also present on cells not of neural crest origin, including chondrocytes,[18] adipocytes,[19] myoepithelial cells, interdigitating cells of lymphoid tissue, Langerhans cells in skin,[20] and T lymphocytes.[21] It is possible that the presence of S-100 protein indicates a common metabolic function.

Table 5 *S-100 protein content of aqueous humour*

Patient	*Disorder*	*S-100 protein (ng/ml)*
1	Melanoma	10
2	Melanoma	10
3	Melanoma	30
4	Melanoma	10
5	Melanoma	10
6	Melanoma	10
7	Normal	120
8	Normal	80
9	Normal	80

SI conversion: ng/ml=µg/l

S-100 protein has been identified in Müller cells and the optic and ciliary nerves of the eye.[22] It is expressed in the majority of primary ocular melanomas[4 23] and is presumably also present, though at low concentrations, in uveal melanocytes. Within the eye potential sources of S-100 protein are therefore limited.

Data obtained from our tumour extraction studies confirm immunohistological studies that demonstrated substantial amounts of S-100 protein in many ocular melanomas. The quantities detected are comparable with those from a cutaneous melanoma and from an ocular glioma (a tumour previously reported to contain S-100 protein), but substantially less than those extracted from most melanoma cell culture lines. It is likely that the quantities obtained from minced tumour extracts are an underestimate, because mechanical disaggregation is a relatively inefficient means of protein extraction. The high yield of S-100 protein from tissue cultures also may reflect synchronisation of the cell cycle. It is known from previous studies that S-100 protein expression is cell cycle stage-dependent,[24] and accumulation of cells maximally expressing S-100 protein at culture confluence is possible. By contrast, tumours in vivo are essentially asynchronous.

Our data support the negative correlation between expression of S-100 protein and melanin, suggested previously on the basis of immunohistology.[18] With immunoperoxidase techniques it is possible that the negative correlation between melanin and S-100 protein might be due to obscuring or quenching of the aminoethylcarbazole developer reaction product, thereby concealing the presence of S-100 protein from visual observation. S-100 protein quantities in tumour extracts, culture extracts, subretinal fluids, and vitreous assessed by radioimmunoassay, however, consistently demonstrated low quantities of S-100 protein in heavily pigmented tumours. These findings strongly support the existence of a negative correlation between melanin production and S-100 protein expression. The biological basis of this negative correlation is unknown.

The quantities of S-100 protein detected in the samples of subretinal fluid varied widely but reached very high levels in some specimens. Subretinal fluid forms in a closed space. Accumulation of tumour derived material, in the absence of a rapid turnover of fluid, may explain why S-100 protein levels observed in subretinal fluids were often higher than those observed in tumour extracts. Very high levels of S-100 protein in subretinal fluid were associated mainly with hypomelanotic tumours Subretinal fluids from eyes without tumours have not yet been examined. It is possible that such fluids would contain detectable S-100 protein derived from melanocytes or Muller cells. It is unlikely, however, that the amount of S-100 protein would reach the very high levels sometimes seen in subretinal fluid from eyes with melanoma.

The quantities of S-100 protein detected in vitreous were not as high as those seen in subretinal fluids, perhaps because of dilution factors due to a larger pool volume and more rapid movement of solutes out of this compartment. The highest levels were associated with moderate to large, posterior, lightly pigmented tumours. Vitreous fluids from patients with tractional retinal detachments had S-100 protein levels above normal. Although well below the level encountered in some melanoma patients, there was more S-100 protein in the vitreous fluids from the three patients with tractional retinal detachment than in vitreous from many tumour patients. It is possible that the protein was released from Muller cells or melanocytes. Aqueous fluids from melanoma patients contained little S-100 protein, as did normal aqueous fluids.

This study demonstrates that low molecular weight tumour-associated molecules can be detected in ocular fluids in nanogram quantities by a readily applicable radioimmunoassay. Secretion of S-100 protein by cells in vitro has not been reported. It is possible that it is released by necrotic melanoma cells. Although the data provide an interesting insight into the relationship of ocular melanoma and the fluids of the eye, the fact that not all ocular melanomas express S-100 protein at a high level and the fact that this molecule does not consistently accumulate at increased concentration in ocular fluids limit the usefulness of S-100 protein quantification in ocular fluids as a diagnostic tool. It is likely, however, that other melanoma-derived molecules, such as those bearing the epitopes detected by several melanoma-directed monoclonal antibodies[2-5] and melanoma-associated, ganglioside-directed monoclonal antibodies,[26] could be identified by this technique These molecules are likely to be more universally expressed by ocular melanoma cells than S-100 protein, and their expression is less likely to be related to the extent of melanogenesis in a given tumour. The detection of such melanoma-associated molecules in ocular fluids might serve as an aid to the diagnosis of intraocular melanomas

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Correspondence

Postmeasles blindness

SIR, The title 'Postmeasles blindness' of an editorial in your journal[1] attracted my attention recently after I had read with absorbed interest the painstaking research on this subject reported by Foster and Sommer from Tanzania in the same issue.[2] This paper goes a long way towards resolving the problem of the nature and relative importance of the interacting factors such as vitamin A deficiency, measles, and herpes simplex infection in causing all too frequently corneal ulceration in young African children.

Imagine my astonishment when I discovered that this paper was not even mentioned in the editorial! The reason for having an editorial at all appears to have been the very slight work of Kogbe and Liotet[3] on tear changes in measles. The authors of the editorial quote only three reports on measles that are by no means typical of results on the subject reported from Africa in recent years. Without quoting any supporting evidence they come to the erroneous conclusions that 'there did not appear to be any correlation between the extent and severity of measles keratitis and nutritional status' and 'suggested that genetic factors contribute to the development of postmeasles blindness.'

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**I have to reject Dr McLaren's criticism of the editorial aspect of this matter. I commissioned an editorial from Dr Monnickendam and Professor Darougar on the paper by Kogbe and Liotet. They were not shown the paper by Foster and Sommer and therefore clearly, were unable to comment on it. The decision to produce an editorial on a particular paper is something I reserve the right to choose for myself as Editor. Editorials are not chosen to reward specially meritorious papers, and I agree that the paper by Foster and Sommer is absolutely excellent. That is why I published it. But editorials are intended to bring to the readers' attention some new or unusual feature which I personally regard as novel or intriguing or otherwise worthy of special comment.
—R J H SMITH

SIR, In response to Dr McLaren's criticism of our editorial[1] we would like to make the following points.

(1) We agree with Dr McLaren that the paper by Drs Foster and Sommer about the causes of childhood blindness in Tanzania[2] is very interesting. We did not refer to it in our editorial because we were not aware of it

(2) In our editorial we attempted to discuss the factors which lead to the development of postmeasles blindness (PMB). There are only a few papers on this subject. We did not discuss measles in undernourished children, since it is well known that it is much more severe in these children than in well nourished children

(3) Malnutrition is common in Africa, Asia, and Central and Southern America, and measles is particularly severe in malnourished children However, PMB is found in some of these countries and not others. In a study of children with measles living in a slum area of Hyderabad, India, PMB was not seen.[3] In Africa PMB is common in some countries but not others. In Tanzania[2] measles was not a common cause of corneal ulceration, and measles alone did not cause blindness In Kenya[4] 10 out of 248 children (4%) with measles developed corneal complications, seven of whom developed large corneal erosions and three of whom developed exposure ulcers. In northern Nigeria[5] measles was the precipitating disease in 63 out of 70 children (90%) with corneal ulceration. A survey of hospital patients with corneal scarring showed that measles caused 42% of all scarring and 54% of bilateral scarring. Corneal ulceration following measles has also been reported in children of African origin living in Haiti.[6] Why do some children develop PMB while others in the same population do not? In Kenya it was reported that 'no association between the extent of severity of keratitis and nutritional status could be found.'[4] Nutritional status was assessed in northern Nigerian children with and without corneal ulceration following measles.[5] There was no difference between the serum prealbumin levels in the two groups of children, while serum retinol-binding protein levels were significantly higher in the children with corneal ulcers than in those without ulcers. These results suggest that the development of PMB was not directly linked with the degree of malnutrition or vitamin A deficiency in these children.

(4) There are two possible explanations as to why there are differences in the prevalence of PMB in different countries of the Third World and why some individuals in a population with a high prevalence of PMB develop the disease while others do not. The first is that there are differences in internal or host factors—i.e., genetic factors; and the other is that there are differences in external factors. The presence of PMB in Africans and its absence in Indians suggests that genetic differences may be important. Possible environmental differences include secondary ocular herpes simplex virus (HSV) infection, which appears to be an important factor in PMB in northern Nigeria.[5] However, it does not appear to be important in East Africa. In Kenya HSV infection was not found,[4] while in Tanzania[2] it was found that, although HSV was associated with 10 out of 48 (21%) cases of corneal ulcers following measles, it caused only one case of blindness. The use of traditional medicines is another external factor which may affect the development of PMB.[2] The development of dry eye appears to be important in PMB It has been reported that the frequent application of tetracycline eye ointment prevented the development of erosions and exposure ulcers in children with measles because the greasy ointment base prevented drying of the corneal and conjunctival surfaces.[4] Nothing is known about the factors which lead to the development of dry eye following measles, but some individuals may have a genetic predisposition and external factors may be important

(5) We attempted to show that at present we do not have a clear understanding of the development of PMB, and to indicate that further studies are needed.

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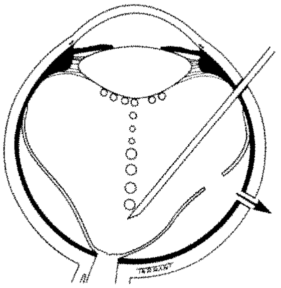
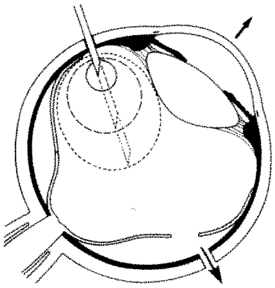


a Posterior injection of gas causes multiple bubbles. b Correct technique after rotation of the globe results in a single bubble injection. The subretinal fluid drainage site is dependent.

b



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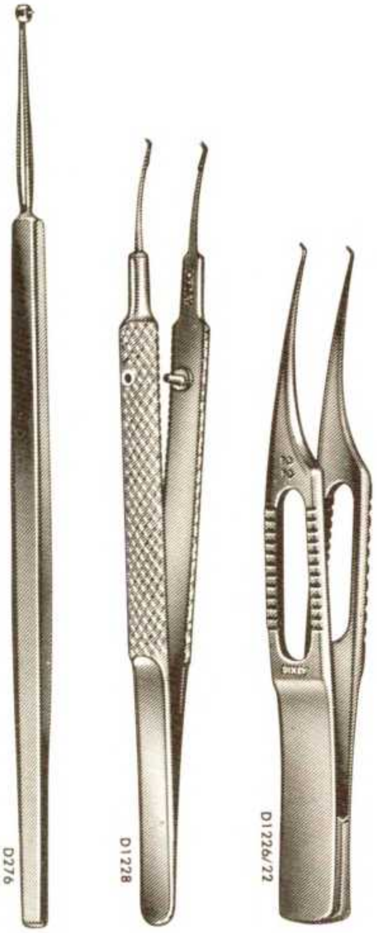

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Contents

A rapid method of grading cataract in epidemiological studies and eye surveys V MEHRA AND D C MINASSIAN *page* 801

A case-control study of cataract in Oxfordshire: some risk factors RUTH VAN HEYNINGEN AND JOHN J HARDING *page* 804

Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide JOHN J HARDING AND RUTH VAN HEYNINGEN *page* 809

Stabilisation of refraction following cataract surgery PETER R BARANYOVITS *page* 815

Surgery of aphakic retinal detachment MOHINDER SINGH *page* 820

Visual after-effects associated with the use of high-resolution visual display units D L SMERDON AND H E WILLSHAW *page* 823

Long-term follow-up of a prospective trial of argon laser photocoagulation in the treatment of central serous retinopathy LINDA FICKER, GILLIAN VAFIDIS, ADRIAN WHILE, AND PETER LEAVER *page* 829

Changing fluorescein angiographic appearance of a subretinal membrane GIUSEPPE GIUFFRÈ *page* 835

Photocoagulation of raised new vessels by long-duration low-energy argon laser photocoagulation—a preliminary study SABAH M ZEKI AND GORDON N DUTTON *page* 837

Evaluation of a non-mydriatic camera in Indian and European diabetic patients R MOHAN, E M KOHNER, S J ALDINGTON, I NIJHAR, V MOHAN, AND H M MATHER *page* 841

Single stage insertion of the Molteno tube for glaucoma and modifications to reduce postoperative hypotony J E A HOARE NAIRNE, D SHERWOOD, J S H JACOB, AND W J C C RICH *page* 846

A case of 'low tension glaucoma' with primary empty sella SHIGEKI YAMABAYASHI, TETSUYA YAMAMOTO, TAKAYA SASAKI, AND SHIGEO TSUKAHARA *page* 852

Spontaneous reformation of upper eyelid HEMANT K MEHTA *page* 856

Blepharochalasis DONALD J BERGIN, CLINTON D McCORD, TIMOTHY BERGER, HOWARD FRIEDBERG, AND WILLIAM WATERHOUSE *page* 863

Testicular cancer presenting as a red swollen lid J A HAM AND N J CARR *page* 868

Bilateral orbital cavernous haemangiomas PETER D FRIES AND DEVRON H CHAR *page* 871

Detection and quantification of S-100 protein in ocular tissues and fluids from patients with intraocular melanoma ALISTAIR J COCHRAN, GARY N HOLLAND, ROMAINE E SAXTON, BERTIL E DAMATO, WALLACE R FOULDS, HARVEY R HERSCHMAN, ROBERT Y FOOS, BRADLEY R STRAATSMA, WILLIAM R LEE *page* 874

Correspondence *page* 879

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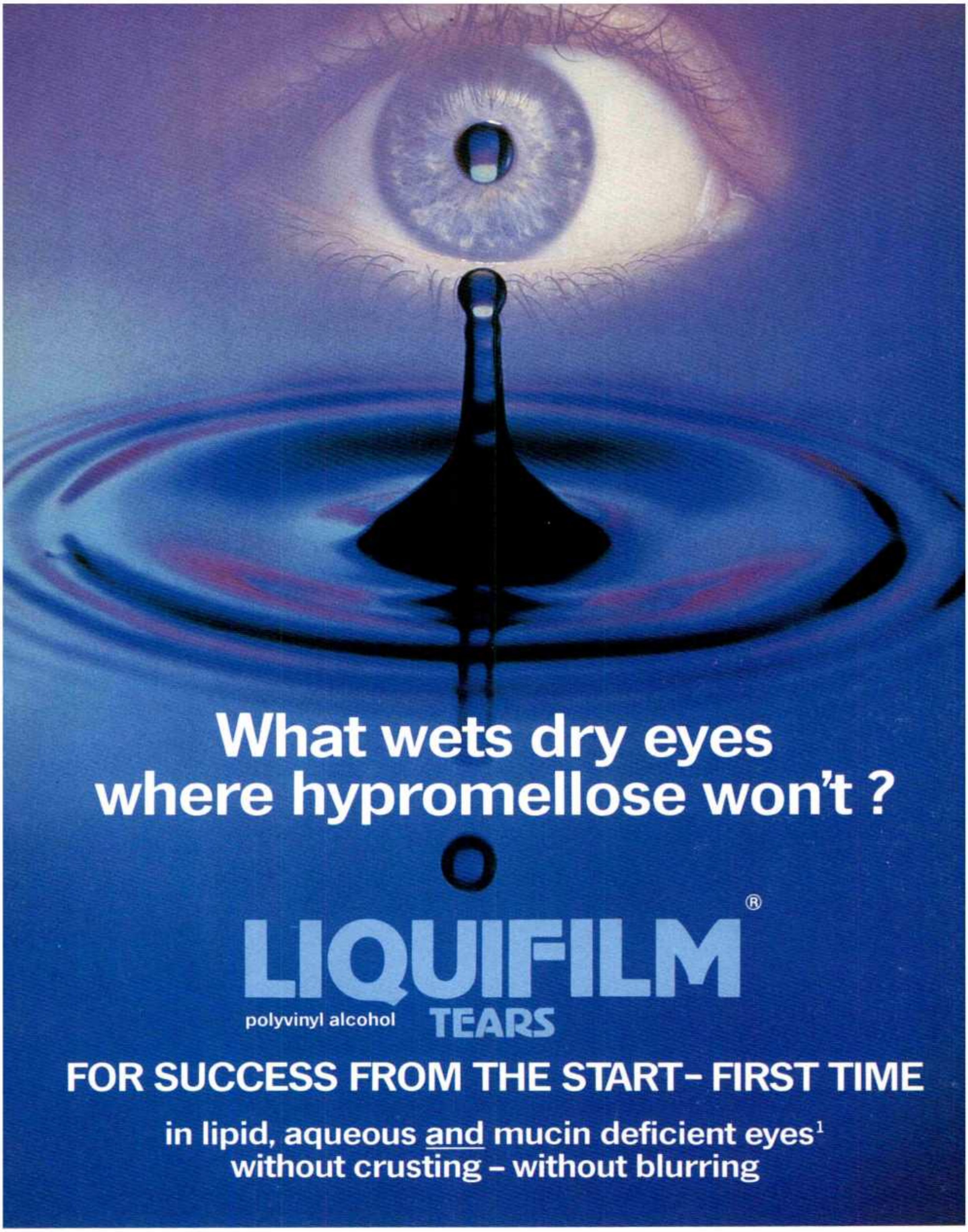
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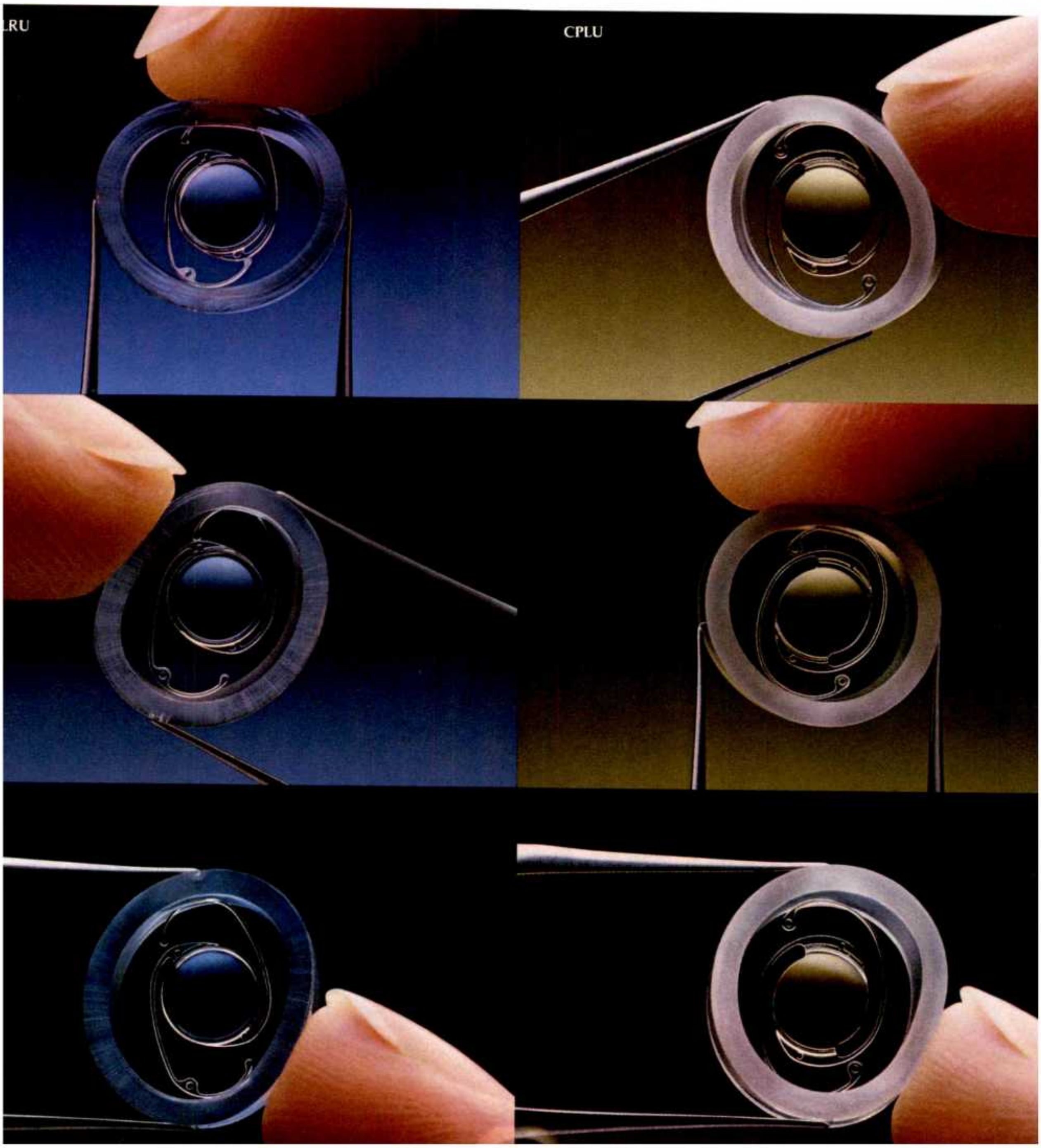

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Early trabeculectomy versus conventional management in primary open angle glaucoma

J L JAY AND S B MURRAY

From the Tennent Institute of Ophthalmology, University of Glasgow, Western Infirmary, Glasgow G11 6NT

SUMMARY The results of a randomised, prospective, multicentre trial of the management of primary open angle glaucoma are presented at up to five years' follow up. Previously undiagnosed cases were selected with intraocular pressure of 26 mmHg or more on two occasions together with field loss characteristic of glaucoma. Analysis was performed on one eye selected at random from each of 99 patients. Conventional medical treatment followed in unsuccessful cases by trabeculectomy (group A) was compared with trabeculectomy at diagnosis followed when necessary by supplementary medical therapy (group B). The life expectancy of these glaucoma patients was found to be similar to that for the local population matched for age and sex. In group A after four years trabeculectomy had been performed in 53% of eyes because medical management had failed to control the disease. The rate of operation was lower in those patients with intraocular pressure less than 31 mmHg and mild relative field loss (17% at three years) than in those with intraocular pressure greater than 30 mmHg and dense scotomas (75% at three years). Early surgery provided much more stable control with fewer changes in treatment than in group A. The group mean intraocular pressure after trabeculectomy was 15·0 mmHg irrespective of the time of operation, and this was significantly lower than the intraocular pressure in those cases thought to be controlled on medical therapy alone at the end of the first year (20·8 mmHg). Early operation provided significantly better protection of visual field, and the extra loss of visual field with delayed operation occurred in the preoperative period. Changes in visual fields were not related to the use of miotics. There was no significant difference in the final visual acuity in the two groups, but six cases in group A lost central fixation because of progressive loss of visual field, and there were no such cases in group B. Cataract occurred in approximately 10% of cases in both groups, but in group A this happened with only half the number of operations and at a shorter postoperative follow-up than in group B. It appears that in cases of primary open angle glaucoma of this severity the risk of delaying operation are significantly greater than those of performing trabeculectomy as the primary treatment.

This is the second report on the progress of a prospective, randomised, multicentre trial of the management of primary open angle glaucoma. Preliminary results were reported in 1983,[1] and data are now available at up to five years of follow-up The aim is to test whether with the increased safety of trabeculectomy over earlier drainage operations it is still justifiable to persist with the conventional practice of using medical therapy as the first line of treatment. Other workers are studying the same question, and it seems agreed that trabeculectomy provides a lower intraocular pressure with less diurnal variation than medical therapy or argon laser trabeculoplasty.[2] In addition, successful surgery avoids the uncertainties of medical therapy associated with the limited duration of each drug application and the possible failure of the patient to use treatment as directed.[3-5] Smith [6,7] has compared the long-term results of medical versus surgical therapy at up to 18 years. His results indicate that drainage surgery is superior to medical therapy in lowering intraocular pressure and that early randomised operation was not detrimental to visual acuity in comparison with cases initially allocated to medical

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therapy. Changes in visual field were less conclusive but did suggest that early operation might have a beneficial effect. It should be noted that this study was carried out on a group with relatively low mean untreated intraocular pressure at diagnosis (25 mmHg) and that there have been more recent major advances in both medical and surgical treatment.

We have therefore compared conventional management, where trabeculectomy is carried out only after demonstrable failure of medical therapy, with primary trabeculectomy, where operation is performed as soon as possible after diagnosis. The results of trabeculectomy in our hands confirm that it is a safe and effective procedure.[11]

Patients and methods

A collaborative trial was set up to study the patients of nine consultant ophthalmologists based in five Glasgow hospitals. All were consecutive and previously undiagnosed cases of primary open angle glaucoma, including those with pseudoexfoliation. Patients were accepted if the untreated intraocular pressure was 26 mmHg (Goldmann) or more on two occasions and if field defects characteristic of glaucoma were present. They were allocated to one of two treatment groups by means of a table of random numbers.

Group A was treated conventionally with up to a maximum of three different topical or systemic drugs. Where maximum tolerated medical treatment was insufficient to control the intraocular pressure or prevent loss of visual field, trabeculectomy as described by Watson[10 11] was performed, usually with local anaesthesia.

Group B had trabeculectomy as soon as possible within four weeks of diagnosis, but preliminary medical therapy was used where necessary to reduce the intraocular pressure to a safe level prior to surgery. In both groups postoperative medical therapy was introduced when indicated according to the usual clinical criteria.

Visual acuity (Snellen), visual field (Tübingen), and intraocular pressure (Goldmann) measurements and optic disc photographs were taken at the Tennent Institute on entry to the trial and at yearly intervals thereafter.

Visual field tests were carried out as part of the standard glaucoma clinic assessment by ophthalmic opticians specially trained as perimetrists. Patients were not separately identified as belonging to a clinical trial. Examinations at appropriate intervening periods were carried out by the referring ophthalmologists, who remained responsible for all decisions in the management of their own patients after the initial random allocation into groups A and B. In cases of group A which eventually required operation the indications for operation were recorded. Surgery was performed in the referring hospital by whichever surgeon was deemed appropriate in the normal practice of that hospital. No attempt was made to limit the operation to selected surgeons. The clinical findings including copies of field charts were sent to the referring ophthalmologist after each annual assessment.

No statement of opinion or advice about past or future management was made. The referring surgeons were not given any fixed criteria for adequate pressure control or significant change in visual field but, as stated above for group A, no patient was to be maintained on more than three separate topical or systemic drugs. In principle the surgeons agreed that a treated intraocular pressure of approximately 20–22 mmHg did not of itself indicate adequate pressure control except where it represented a marked reduction from the pretreatment level in an eye with mild field loss or cupping. They made their own clinical decisions about the significance of visual field changes based on the field tests carried out in their own hospital supplemented by the annual results supplied by the trial investigator.

A simple punched card sorting system was used to store and analyse the following details of patients at entry to the trial: sex, age, general health, initial symptoms or reason for diagnosis, visual acuity, visual fields, maximum intraocular pressure before treatment, and appearance of the optic discs. Each year further information was entered about changes

Table 1 *Classification of visual field changes*

Stage	*Visual field loss*
1	Early relative defects (to 1 0/10 asb Tubingen, equivalent to I-2e Goldmann) in arcuate area or nasal step
2	Absolute defects (to 1 0/00 asb Tubingen, equivalent to I-4e Goldmann) outside 10° of fixation in all quadrants
3	As stage 2 but encroaching between 5° and 10° from fixation in 1 to 4 quadrants
4	As stage 2 but within 5° of fixation in 1 to 3 quadrants
5	As stage 2 but within 5° of fixation in all quadrants

Table 2 *Classification of optic disc changes at diagnosis and the percentage distribution within each group*

Grade	*Optic disc appearance*	*Group*	
		A	*B*
1	C/D≤0·6	25%	30%
2	Suspicious shape of optic cup but C/D≤0·6	6%	4%
3	Pathological, 0·6<C/D<0·9	29%	28%
4	End Stage, C/D>0·9	40%	37%

C/D=Vertical cup to disc ratio

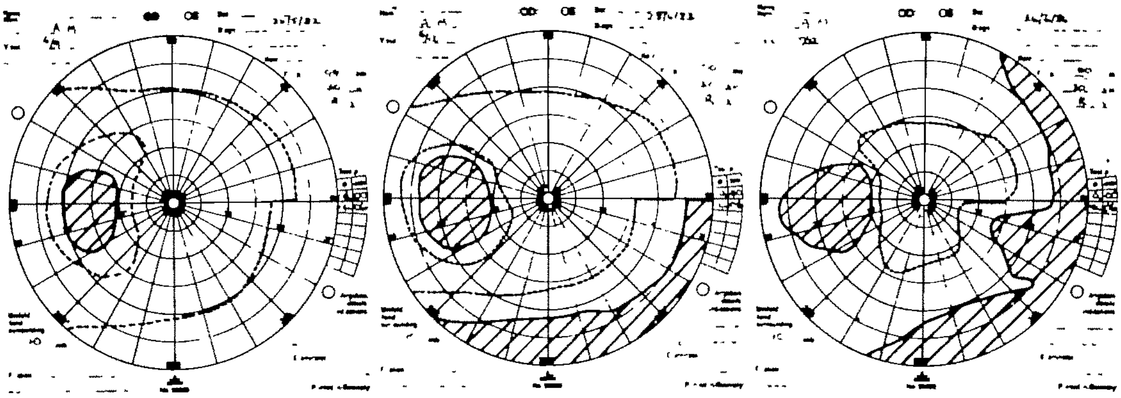

Fig 1 *Annual visual field tests illustrating* (left) *stage 1 field changes in 1982,* (centre) *progressing to stage 2 by 1983,* (right) *further significant change by 1984 but remaining in stage 2 of the classification*

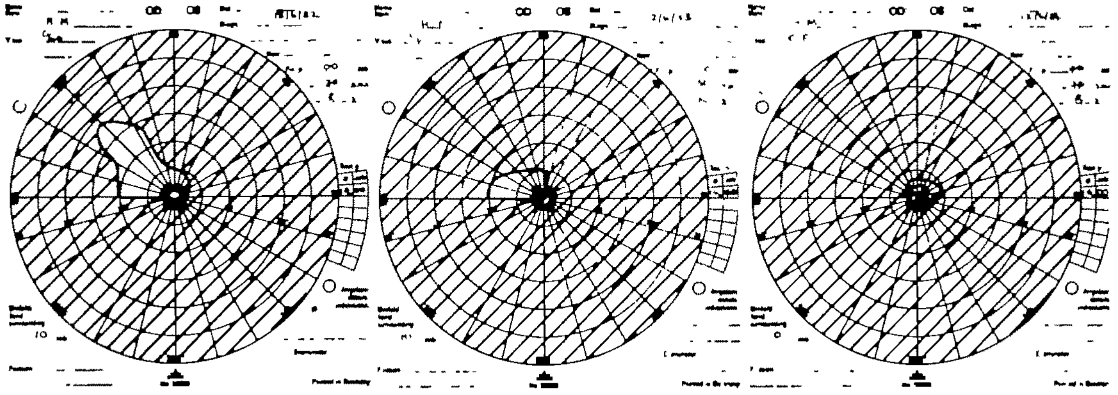

Fig. 2 *A more severe example commencing* (left) *in stage 4 of the visual field classification in 1982,* (centre) *showing significant progression within stage 4 by 1983, and* (right) *further progression into stage 5 by 1984*

in visual acuity, visual fields, intraocular pressure, disc appearances, and management. To simplify the records an arbitrary classification of the visual field changes was devised as shown in Table 1 and the optic disc changes were graded as shown in Table 2. Table 2 also shows the distribution of optic disc changes in each group. The change in visual field at yearly intervals was assessed by an experienced observer familiar with the expected variation in the test system. Any significant alteration in density or area of field loss was noted, and separate data were recorded for cases with more severe field change causing deterioration by one stage or more.

Figs. 1 and 2 illustrate the classification of field loss and the amount of change which was considered significant. Examples of change within a stage of the classification as well as across stage boundaries are given. Where both eyes of a patient were included in the trial, one was selected at random for the analysis of results.

To discover whether the extra loss of visual field of group A over group B had occurred before or after the delayed trabeculectomy, the 26 group A eyes which had required operation were paired with eyes selected from group B to have a comparable period of postoperative follow-up. This selection was necessary because the whole group could not be used, since the available postoperative follow-up period for group A was shorter than for group B. The pairs were matched in order of priority for: stage of visual field at diagnosis (100% match), duration of postoperative follow-up (100% match), intraocular pressure at diagnosis (92% match with ±20% of pressure at diagnosis and 50% match with ±10% of pressure at diagnosis), age (46% match within 10 years), and sex (80% match).

To take account of the improvement in visual field which may occur with therapy a simple digital scoring system was used. Increase or decrease of field within a stage was awarded + or −0·5, and for each stage boundary crossed + or −1·0. Statistical analysis was performed with the Minitab package of the University of Glasgow computer using t, χ^2, and nonparametric tests as appropriate. The main features of each group were compared at diagnosis and at each year of follow-up.

A life table was constructed for the patients under study and compared with the life expectancy of the local population.

Results

Patients were recruited at a rate of approximately 25 per year. Ninety-nine completed at least one year in the trial, 53 in group A and 46 in group B. Another four patients initially allocated to group B refused operation and were excluded from the analysis. The mean age at diagnosis was 67·4 years for group A and 64·3 years for group B, and the group mean intraocular pressure at diagnosis was 35·9 mmHg for group A and 36·1 mmHg for group B. There was no significant difference between the groups at the start of the trial for sex ($0{\cdot}05<p<0{\cdot}1$), age ($0{\cdot}1<p<0{\cdot}2$), right or left eyes ($p>0{\cdot}5$), visual acuity ($0{\cdot}05<p<0{\cdot}1$), visual fields ($p>0{\cdot}5$), optic discs ($p>0{\cdot}05$), intraocular pressure ($p>0{\cdot}5$), or incidence of systemic disease ($p>0{\cdot}5$). The Mann-Whitney test was used for age and intraocular pressure, χ^2 for other factors. The mean time of latest follow-up was 30 months for group A and 33 months for group B.

Table 3 shows the numbers available at each year of follow-up. Those known to be dead are indicated, and one patient was lost to follow-up. Life table analysis showed that the number dying (12 males, 4 females) was not significantly different ($p>0{\cdot}2$, Poisson distribution) from that expected in the local population matched for age and sex (14·1 males, 6·7 females). Between group A and group B the death rate was comparable.

Table 4 shows the frequency and timing of operation in group A (conventional management) in those eyes where satisfactory medical control was not possible. The rate for the whole group increased from 32% at one year to 53% at four years, but medical therapy was more likely to be abandoned in the more severe cases. Thus in cases of milder disease, arbitrarily defined at diagnosis as intraocular pressure <31 mmHg with stage 1 field loss, those requiring operation increased from 8% at one year to 17% at three years. In cases of more severe disease, an intraocular pressure >30 mmHg and having absolute field defects (stage 2 or more, see Table 1), the operation rate was 58% at one year and 75% at three years. Further stratification to identify the worst cases (>35 mmHg; Field stage 3 to 5) indicated a slightly higher rate of operation, 63% at one year and 78% at three years.

The reasons given by the referring surgeon for

Table 3 *Patients available for study at end of each year, indicating numbers dead or lost to follow-up*

At end of year	*No available for study*		*No dead*			*% Dead*	*Lost to follow-up*
	A	*B*	*A*	*B*	*A+B*		
1	53	46	1	3	4	4	0
2	36	39	4	3	7	9	1
3	25	24	4	3	7	12	1
4	15	15	2	1	3	9	0
5	5	3	1	1	2	20	0

Table 4 *Percentage of eyes in group A having trabeculectomy because of failure of medical control. The figures indicate cumulative data from diagnosis to the end of the year stated. Very few cases with IOP >30 mmHg and with field loss more advanced than stage 1 at diagnosis have avoided operation at the end of the second and third years*

At end of year	*Whole group*	*Stratified by severity of disease at diagnosis*		
		IOP <31 mmHg and field stage 1	*IOP >30 mmHg and field stage 2–5*	*IOP >35 mmHg and field stage 3–5*
1	32%	8%	58%	63%
2	47%	33%	60%	80%
3	52%	17%	75%	78%
4	53%	Numbers insufficient for analysis		

Table 5 *Indications for abandoning medical therapy and proceeding to trabeculectomy in group A*

Time from diagnosis to operation (months)	*n*	*Indications for operation*			
		Uncontrolled IOP	*Uncontrolled IOP and increasing field loss*	*Controlled IOP but increasing field loss*	*Other*
0–3	6	6	0	0	0
4–12	11	6	2	3	0
13–24	6	0	3*	2	1†
25–33	3	2*	1	0	0

*One of these patients identified with poor compliance
†Intolerant of all medical therapy

Table 6 *Eyes requiring changes of therapy during each year*

Year	*Group A*			*Group B*		
	n	*Extra medical therapy*	*Operation*	*n*	*Extra medical therapy*	*Operation*
1	53	16	17	46	7	(46)
2	35	5	6	39	1	0
3	25	5	3	24	2	0
4	14	4	0	15	0	1

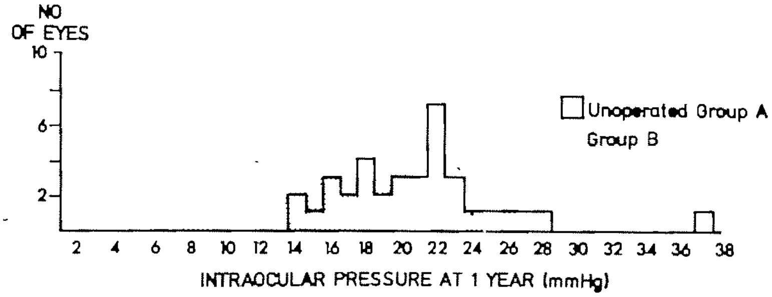

Fig. 3 *Histogram comparing the intraocular pressure at one year achieved by medical therapy in group A eyes which were thought to be controlled without surgery (mean=20·8 mmHg) and the pressure in group B who had trabeculectomy at diagnosis (mean=15·0 mmHg). None of the patients in group B were using supplementary medical treatment.*

proceeding to operation in these group A eyes are set out in Table 5. Unacceptably high intraocular pressure was the only indication for operation within three months of diagnosis; thereafter progressive loss of visual field with or without recognised high intraocular pressure became more frequent. The proportion of group A cases proceeding to trabeculectomy in the first year after entry was examined for each year of the trial to determine if the referring surgeons were changing their indications for abandoning medical therapy. There was a slight increase in the rate of operation in group A in the later years, but this was not significant ($p>0{\cdot}5$; χ^2).

To compare the relative effectiveness of medical therapy with trabeculectomy in reducing intraocular pressure, the pressures in those eyes in group A on medical therapy which had not required operation were compared with the pressures in group B. None of Group B were having supplementary medical treatment at the time of this comparison at the end of the first year, though some did require supplementary therapy thereafter (Table 6). The 32% of group A where medical control had already proved impossible (Table 4) are not included. Fig. 3 displays the lower intraocular pressure achieved by trabeculectomy (mean=15·0 mmHg) compared with those apparently controlled on medical therapy alone (mean=20·8 mmHg). The difference is significant ($p<0{\cdot}001$, Mann-Whitney). Of the nine patients in group A with intraocular pressure 22 mmHg at this examination three were not using eyedrops as directed and another three were judged to be unsatisfactory and had their treatment changed. The raised pressure in these six eyes identified at the one-year assessment was unexpected and much higher than previously noted by the referring surgeon (the remaining three eyes were known to have treated pressures in the region of 22 mmHg, which was considered acceptable by the referring ophthalmologist). Even if these six eyes are excluded from the group A data to obtain a group mean intraocular pressure of those judged well enough controlled after this examination to continue with unchanged treatment, the mean pressure of 19·5 mmHg is still significantly higher than all group B eyes at one year ($p<0{\cdot}001$, Mann-Whitney).

The mean intraocular pressure after trabeculectomy without supplementary medical therapy was identical whether the operation was carried out as a primary procedure (group B) or only after failure of medical therapy (group A). In both cases the mean pressure was 15·0 mmHg.

Figs. 4 and 5 display changes in visual field of at least one full stage of the classification from diagnosis to latest follow-up. The data for group A include those eyes which could not be controlled by medical means and which eventually required operation. Comparison of the figures confirms that group A showed more frequent and more severe loss of visual field than group B. Application of the Mann-Whitney test to take account of the numbers showing change and the degree of change in each case shows these differences are significant ($0{\cdot}02<p<0{\cdot}05$). The risk of progression of field defects was not related to the severity of loss at diagnosis; those with mild field defects were just as likely to have progressive deterioration as those with advanced disease.

Several patients showed improvement in visual field with treatment, but this was more common and more marked in Group B. The changes in visual field cannot be explained by variations in miotic therapy. All initial field tests were performed before starting treatment, and in group B no eyes were on miotic therapy at the latest examination. In group A 13 eyes were on pilocarpine at the latest follow-up, but, of these, six showed field tests which were unchanged or improved and another six showed field deterioration which had occurred before the introduction or during stable dosage of pilocarpine.

Tables 7 and 8 show the percentage of eyes in each group with visual field deterioration from diagnosis to the end of each completed year. Any field change judged to be significant by an experienced observer is included for Table 7, but only the more strict criteria, loss of field severe enough to transfer from one stage of the classification to another, are considered for

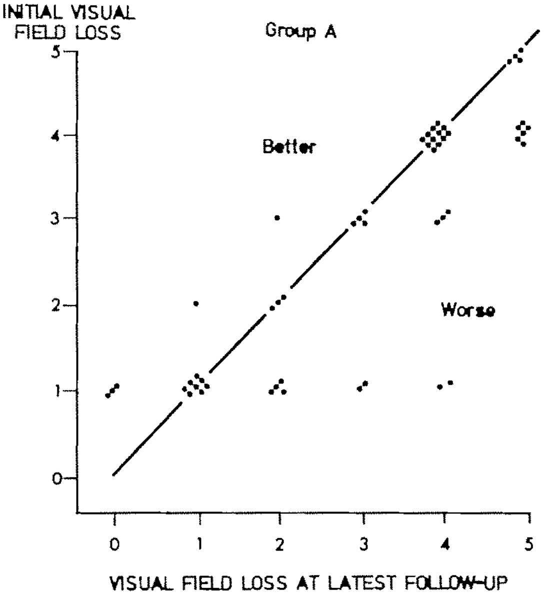

Fig. 4 *Visual field change at latest follow-up (mean=30 months) in all group A eyes.*

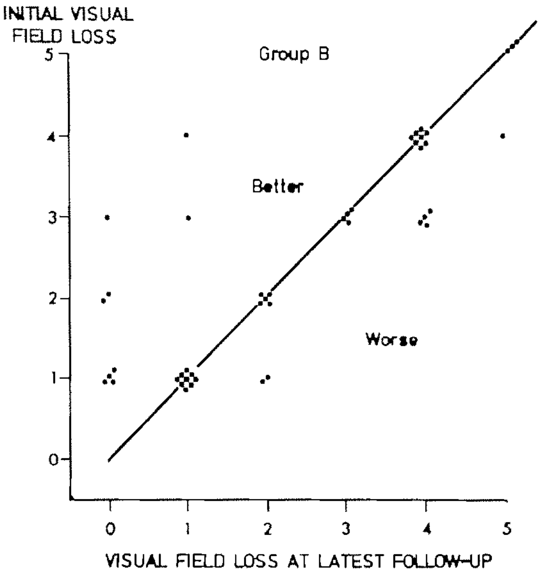

Fig. 5 *Visual field change at latest follow-up in group B (mean=33 months). Comparison with Fig. 2 shows the detrimental effect of delaying operation until medical therapy is seen to be unsuccessful. Group B is significantly different from group A ($0\cdot02<p<0\cdot05$).*

Table 8. It therefore represents those eyes with more serious and sight threatening deterioration. By both standards of assessment approximately twice as many eyes in group A lost field as in group B at each year of follow-up. p Values by χ^2 test are indicated.

To determine whether the increased loss of field of group A over group B had occurred before trabeculectomy, and during the trial of medical treatment rather than after operation, the relative performance of the matched pairs was analysed by the digital scoring system. There was no significant difference between the two groups for postoperative field damage ($0\cdot2<p<0\cdot5$, Wilcoxon signed rank test), but the preoperative field loss for group A was greater than the postoperative loss ($0\cdot1<p<0\cdot02$, Mann-Whitney test) (Table 9). Using a change of vertical cup to disc ratio of $\pm0\cdot1$ or more, we found no significant difference in the appearance of the optic discs of each group at latest follow-up, but the trend favoured group B.

Very few eyes showed change in corrected Snellen visual acuity of more than one line (Figs. 6 and 7). The slightly greater number in group A with reduced acuity of more than one line is not significant ($0\cdot2<p<0\cdot5$, χ^2). Nevertheless this overall assessment hides important changes in group A, as six eyes in this group lost central fixation because of progressive field loss—four in the first year, one in the

Table 7 *Percentage of eyes in each group showing deterioration in visual fields from time of diagnosis to end of year stated*

At end of year	*Percentage losing field from time of diagnosis*				
	Group A		*Group B*		χ^2
	n	*%*	*n*	*%*	
1	53	51	46	20	$0\cdot001<p<0\cdot01$
2	36	55	39	25	$0\cdot01<p<0\cdot02$
3	25	60	24	25	$0\cdot01<p<0\cdot02$
4	15	53	15	33	Not significant*

*Numbers too small for valid analysis.

Table 8 *Percentage of eyes in each group showing deterioration in visual field by one stage or more from time of diagnosis to end of year stated*

At end of year	*Percentage losing field by one stage or more from time of diagnosis*				
	Group A		*Group B*		χ^2
	n	*%*	*n*	*%*	
1	53	26	46	9	$0\cdot02<p<0\cdot05$
2	36	25	39	15	Not significant
3	25	36	24	8	$0\cdot02<p<0\cdot05$
4	15	40	15	20	Not significant*

*Numbers too small for valid analysis.

Table 9 *Digital score for visual field change for the 26 eyes in group A which eventually required operation compared with 26 matched controls from group B*

Group	*Net score*	*p*
Group A. Preoperative change	−10·0	0·018 (significant)
Group A. Postoperative change	−1·0	0·266 (not significant)
Group B. Postoperative change	−4·5	

second, and one in the third year. There were no comparable events in group B. Progressive lens opacity, usually nuclear sclerosis, was the only other cause of reduced visual acuity. These progressive cataracts were more likely to arise in previously normal lenses than in the 20% of cases which showed incipient cataract before glaucoma treatment. The overall 10% incidence of cataract producing reduction of more than one line in visual acuity was similar in the two groups (Table 10). Of the six cases of cataract in group A one appeared before operation. Although the incidence of cataract in group A was similar to that in group B, this occurred in a group with fewer operations (53% at three years, Table 4), and the average postoperative follow-up time for those who did have operation in group A (22 months) was shorter than that in group B (33 months). The numbers with cataract, however, were too small for valid statistical comparison.

Discussion

This clinical trial was designed not to test the intrinsic merits of surgical or medical therapy but to discover the sequence in which they should be used. The results provide a basis for the assessment of risks and benefits of trabeculectomy as primary treatment with secondary support from medical therapy compared with the hitherto more conventional reverse sequence. The multicentre design of the study makes it more relevant as a guide to other surgeons who might otherwise remain sceptical of results from one individual, who might be considered to have greater or lesser skills in medical or surgical management. We therefore feel that our trial is a valid test of the two treatment strategies as they might be applied in the average glaucoma clinic in the United Kingdom.

Only cases with initial intraocular pressure of 26 mmHg or more were studied, and therefore the findings should not be extrapolated to the glaucoma population with lower pressures. For the severity of glaucoma studied it is clear, however, that the initial attempt at medical control in group A merely delays trabeculectomy in many cases. This delay has been identified by others,[12] and it is a criticism which also applies to argon laser trabeculoplasty.[13] Where the initial intraocular pressure is over 30 mmHg with dense, though not necessarily extensive, field defects, over 75% of cases treated conventionally (group A) require trabeculectomy within three years.

This delayed operation is just as effective as primary surgery in reducing intraocular pressure, and in both cases operation is more effective at doing so

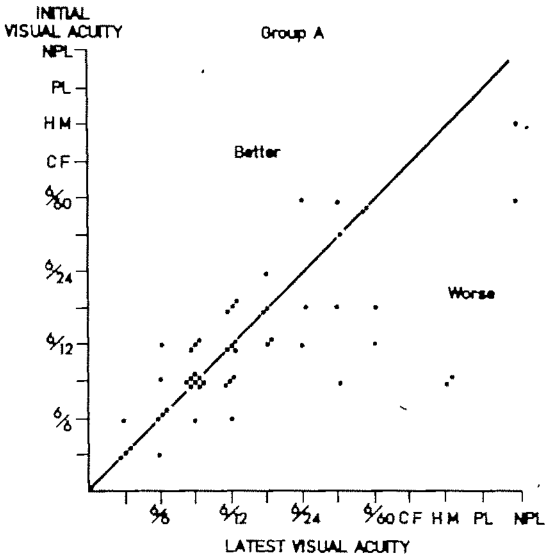

Fig. 6 *Change in visual acuity from diagnosis to latest follow-up in group A (mean=30 months) Six cases lost central fixation because of progressive visual field loss*

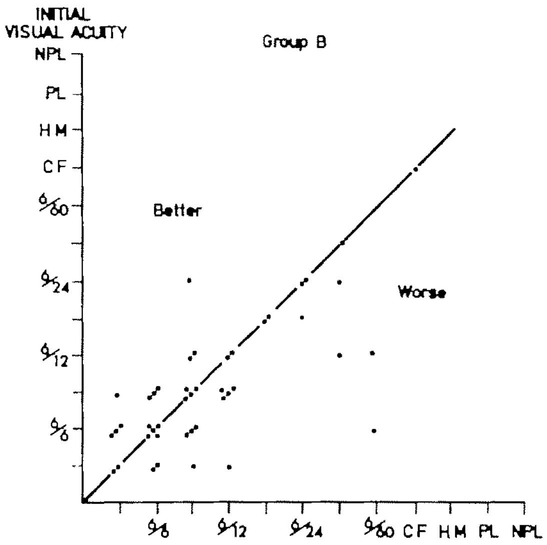

Fig. 7 *Change in visual acuity from diagnosis to latest follow-up (mean=33 months) in group B Although the data are not statistically different from those of group A, no group B eyes lost central fixation.*

Table 10 *Data for cataract at diagnosis and at final follow-up. The incidence is similar in the two groups, but group A had had only half the number of operations and has a shorter postoperative follow-up*

Group	*n*	*Cataract at diagnosis*	*Progressive cataract reducing vision >1 line*			*Mean postoperative follow-up*
			Pre existing	*New*	*Total*	
A	53	11	1	5	6	22 months
B	46	9	2	3	5	33 months

than modern medical therapy. Although delay does not compromise the pressure reducing effect of the operation, it does jeopardise preservation of visual field. Twice as many patients in Group A lose field and to a more severe degree than group B. The frequency of postoperative field loss with normal pressure after early surgery in this study is comparable to that noted by Kidd and O'Connor[14] in their study of field loss after trabeculectomy as part of conventional management. This confirms that, even with surgery successfully reducing intraocular pressure, there is further loss of field in some cases. If this is, as it seems, a slow and at present untreatable deterioration, every chance must be taken to achieve optimum conditions as quickly as possible, and the results presented here suggest for the first time that a trial of initial medical therapy is an unacceptable risk which may allow unnecessary extra deterioration in visual field. We are unable to predict at diagnosis those patients who will show progressive visual field loss[15 16] and therefore cannot accurately select those for whom medical (or laser) therapy will be adequate.

The crude categories of field loss used in this study are not as elegant as more detailed mathematical analysis, but they may be defended as they divide the study population evenly across the 5 stages chosen. Of greater value is that they mark steps in a progression which are clearly significant in the progress of a glaucoma patient. Practising clinicians may therefore find this visual field analysis to be of important clinical as well as statistical significance.

Many surgeons are hesitant to operate early because they believe postoperative cataract may eventually jeopardise visual acuity, and in a very few cases there may be more dramatic surgical complications. Our results indicate no difference in visual acuity between the trial groups at present follow-up. Although numbers are small, with cataract appearing in only 10%, the trend of the data suggests that group A develop cataract just as often as group B despite having only half the number of operations and shorter postoperative follow-up. This may indicate that either medical therapy is equally cataractogenic or the delayed operation carries an increased risk over early operation. More data are required to clarify this point. It is surprising that, where progressive cataract has occurred, it is usually as a new feature and not in those eyes showing early cataract before treatment.

Where less than perfect supervision is available, the poorer performance of the conventional treatment plan may be even more marked, as there may be delay in recognition of unsatisfactory intraocular pressure or deterioration of visual field. In many countries prolonged medical therapy and close supervision are impossible, and surgeons already practise early trabeculectomy. It now seems evident that this may also be the better policy even when close supervision of medically treated patients is possible. Indeed the conditions of the trial are such that it may have provided closer than normal supervision of medical treatment. The annual assessment by the trial investigator may have provided extra data or merely extra incentive for the referring surgeon to look more closely at each case. Again it must be emphasised that these results apply to the more severe cases of established glaucoma. A different strategy may be appropriate for less advanced cases. Before individual surgeons adopt the policy of early operation it is essential that their own surgical results are seen to be as safe and effective as in the published literature.

We thank the following for allocating patients to the trial. Dr T Barrie, D J S Cant, D J Dudgeon, Professor W S Foulds, Professor J V Forrester, Dr P M Kyle, Dr M LeMay We are indebted to Miss Pauline Johnston for typing the manuscript and to Dr D Allan for help with statistical analysis. Dr John Clarke, Information Services Unit, Greater Glasgow Health Board, performed the life table analysis.

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The 12-hour control of intraocular pressure on carteolol 2% twice daily

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SUMMARY In a 15-week double-blind, placebo-controlled, crossover study both carteolol 2% and timolol 0·5% produced a significant reduction in intraocular pressure. Twelve hours after administration the reduction in pressure on carteolol was significantly less than that obtained on timolol.

Carteolol is a non-specific beta-blocking agent used in the treatment of glaucoma. The literature on the effect of carteolol on intraocular pressure is not extensive. Previous publications have demonstrated a significant reduction in pressure at peak effect[1] and for up to six[2] and eight[3] hours. In this placebo controlled study the 12-hour control of intraocular pressure of carteolol 2% and timolol 0·5% are compared.

Material and methods

Twenty-five subjects between the ages of 45 and 80 years were recruited for this trial, 16 male and nine female. All had a mean intraocular pressure of 21 mmHg or more recorded on at least two occasions before the trial began. Exclusion criteria were: open-angle or closed-angle glaucoma, visual field defects detectable with the Friedman analyser, visual acuities of less than 6/12, asthma, cardiac failure, or any other medical condition in which treatment with a beta-blocking agent would be contraindicated. Ethical approval was obtained from the local hospital ethics committee.

At enrolment each patient filled out a medical questionnaire and gave written informed consent. Corrected visual acuities were measured with a Snellen chart, and visual fields were assessed with a Friedman visual field analyser. All subjects on prophylactic ocular hypotensive therapy had this stopped one month before the start of the trial.

Subjects were randomly allocated among six treatment groups, representing all six possible sequences of the three treatments carteolol, timolol, and placebo. The order of administration of the three treatments for each group are given in Table 1.

The study was performed double-masked; the three treatments were presented in identical glass bottles with sterile droppers. Each treatment was instilled into both eyes 12-hourly for one week. There was a four-week washout period between the treatment periods. Intraocular pressures were measured at the beginning of each treatment period, to allow an estimate of the carry-over effect, and 12 hours after the last dose at the end of the treatment period. All measurements were made at the same time of day (to within 14 minutes for each subject) by the same observer.

The intraocular pressures obtained on each of the three treatments were compared by analysis of variance, and pairwise differences between treatments were then identified.

Results

Two subjects failed to complete the study: one completed one treatment period, the other completed two treatment periods. One subject was withdrawn from the study after one week's treatment

Table 1 *The order of administration of treatments in each of six treatment groups*

Group	*1*	*2*	*3*	*4*	*5*	*6*
Treatment 1	T	C	P	T	C	P
Treatment 2	C	T	C	P	P	T
Treatment 3	P	P	T	C	T	C

Carteolol=C. Timolol=T. Placebo=P

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Table 2 *Comparison of the effects of carteolol, timolol, and placebo on intraocular pressure; adjusted for carry-over; 25 subjects, both eyes averaged. Adjusted means in mmHg: carteolol 17·2, timolol 15·7, placebo 19.9*

Comparison	*Estimate*	*SE*	*95% confidence interval*	*% reduction*	*t*	*p*
C vs P	−2·67	0·72	−4·12 to −1·22	−13·4	−3·72	<0·001
T vs P	−4·22	0·73	−5·70 to −2·74	−21·2	−5·75	<0·001
C vs T	+1·55	0·73	+0·07 to +3·03	–	+2·11	<0·05

Carteolol=C Timolol=T. Placebo=P.

with carteolol and a one-month washout owing to the development of a unilateral uveitis and a consequent reduction of visual acuity in the affected eye to 6/24.

The results of the comparison of the effects of carteolol, timolol, and placebo on intraocular pressure are summarised in Table 2. The analysis of variance was performed with the post-treatment intraocular pressure (average of both eyes) as the dependent variable and subject, period, and treatment as the explanatory factors. There was a linear period effect, a reduction of the order of 1·3 mmHg per treatment period. Adjustment for carry-over had very little effect on the results owing to the balanced design of the study.

There was a highly significant reduction in intraocular pressure on both carteolol and timolol. After one week's therapy the reduction in pressure obtained 12 hours after the administration of carteolol 2% was significantly less than that obtained on timolol 0·5%. In the analysis incorporating adjustment for carry-over there was a 13·4% reduction on carteolol and a 21·2% reduction on timolol compared with the mean pressure on placebo.

Discussion

Carteolol is a non-specific beta-blocking agent recently licensed in the UK for use in the treatment of glaucoma. Though the manufacturers suggest a twice daily regimen, there is no satisfactory information so far on the control of intraocular pressure over a 12-hour period.[1]

There is no doubt that at peak effect carteolol 2% does produce a significant reduction in intraocular pressure.[1-3] The difference between the effects of carteolol 1% and carteolol 2% is small and did not reach significance in a crossover study.[4] When comparing the pressures obtained on carteolol with those on placebo (rather than comparing pressures on carteolol with pretreatment pressures, and ignoring the effect of diurnal variation) Kitazawa *et al.* demonstrated a significant reduction in intraocular pressure for up to six hours.[2]

In an open study on eight patients with ocular hypertension and glaucoma Horie *et al.*[5] demonstrated a greater reduction in intraocular pressure on timolol 0·5% than on carteolol 2%. In the same publication the authors reported a failure to demonstrate a difference between timolol 0·5% and carteolol 2% in a double-blind study on 10 subjects. This might have been due to the small sample size or to the study design, in which the two treatments were administered in succession (for one month each) without an intervening washout period.

The present study is the first placebo-controlled, double-masked trial to show a significant reduction in intraocular pressure 12 hours after the administration of carteolol 2%. It also shows that the reduction on carteolol 2% is significantly less than that obtained on timolol 0·5%.

The results presented here apply to 'glaucoma suspects' who have had one week's treatment with carteolol and with timolol. Further work is needed to determine the reduction in pressure obtained over longer treatment periods, and, more important, to determine the long term effects of carteolol on the visual field of glaucoma patients. Until the initial studies on the effect of carteolol on differential light threshold are confirmed,[6] carteolol, in terms of its ocular effect, does not appear to offer any significant advantage over timolol. In terms of the 12-hour control of intraocular pressure carteolol appears to be less effective than timolol.

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Levobunolol compared with timolol: a four-year study

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SUMMARY Fifty-one patients with raised intraocular pressure (IOP) were treated for up to four years with one of three ophthalmic solutions: 0·5% levobunolol, 1% levobunolol, or 0·5% timolol. The study was conducted as a double-masked, randomised trial in which medications were administered twice daily to both eyes. Levobunolol and timolol were equally effective in reducing overall mean IOP; reductions were greater than 8·8 mmHg in all three treatment groups. The study showed levobunolol to be as safe and effective as timolol in the long-term control of raised IOP.

Glaucoma is a chronic disease, generally requiring a lifetime of treatment. Most evaluations of new agents, however, are of relatively limited durations. In the present report we describe our findings in a four-year, double-masked comparison of levobunolol, a new β_1/β_2-adrenoceptor antagonist, and timolol. This is a follow-up to our previous one-year report of this comparison.[1]

Subjects and methods

As detailed previously,[1] this was a randomised, double-masked comparison of three treatments: 0·5% levobunolol, 1% levobunolol, or 0·5% timolol. All were administered twice daily into both eyes. Patients with chronic open-angle glaucoma or ocular hypertension characterised by untreated IOP values of 23 mmHg or higher in both eyes were considered for the study. Excluded from participation were patients with contraindications to the topical or systemic use of beta blockers, those with secondary or narrow-angle glaucoma or aphakia, and those who had used systemic beta blockers within the three months immediately preceding the study.

The study consisted of 35 visits including a baseline examination. After the baseline examination and as close as possible to 9 am the patients received a single drop of the test medication into each eye. They were then instructed to administer a single drop of the study medication into each eye twice daily (9 am and 9 pm) for the duration of the study. The cup-disc ratio was measured subjectively with a direct ophthalmoscope and visual fields by Goldmann kinetic perimetry.

IOP values for right and left eyes were averaged for analysis. Owing to differences at baseline an analysis of covariance model (ANCOVA) was used to analyse mean changes of IOP from baseline.[2] Within-group changes from baseline were tested for significance with the paired *t* test. Overall mean changes from baseline were tested by analysis of variance (ANOVA) for repeated measures design.[3] Kaplan-Meier survival curves were used to evaluate time to treatment failure due to uncontrolled IOP.[4] Survival curves were compared among the groups by the log-rank method.[5] Results were considered statistically significant if p values were ≤0·05.

Results

Fifty-one patients participated in the study. One patient was diagnosed as having ocular hypertension; the rest had open-angle glaucoma. Other demographic characteristics are presented in Table 1.

As shown in Fig. 1, the cumulative probability of successful control of IOP (life-table analysis) for four years was approximately 40% for each treatment group. There was no significant difference among

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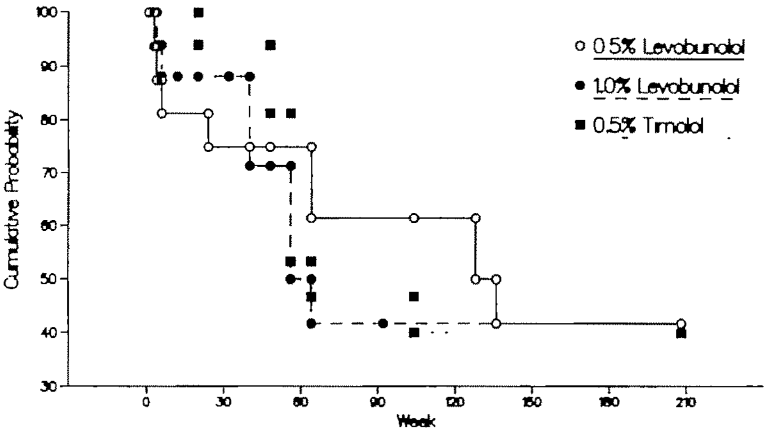

Fig. 1 *Cumulative probability of successful control of IOP approximately 40% in each treatment group.*

groups. Most of the efficacy failures occurred within the first two years of the study.

The status of all the patients at the end of the study is shown in Table 2. In addition to the patients whose treatment was terminated owing to inadequate control of IOP, approximately 8% had their treatment terminated for drug-related adverse effects. These were in the two levobunolol groups and included three reports of topical allergies to levobunolol and one report of dyspnoea. All adverse effects occurred after approximately one year of treatment.

As shown in Fig. 2, there was a significant decrease of mean IOP from baseline in all three treatment groups throughout the four years of the study. Overall, the mean decrease in IOP was 9·5 mmHg, 9·6 mmHg, and 8·8 mmHg in the 0·5% levobunolol, 1% levobunolol and 0·5% timolol groups, respectively. There were no significant differences among the groups.

Table 1 *Study population**

Variable	*0·5% Levobunolol (n=17)*	*1% Levobunolol (n=17)*	*0·5% Timolol (n=17)*
Age (years)			
Mean±SD	70·9±6·9	70·8±9·1	69·1±6·7
Sex			
Male	10	10	12
Female	6	7	5
Not reported	1	0	0
Iris colour			
Blue	0	1	3
Green	6	7	6
Brown	11	9	8
Glaucoma diagnosis			
Open-angle glaucoma	16 (94%)	17 (100%)	17 (100%)
Ocular hypertension	1 (6%)	0 (0%)	0 (0%)

*No significant differences among the groups were noted.

Table 2 *Status of patients at end of four years*

	0·5% Levobunolol	*1% Levobunolol*	*0·5% Timolol*	*Total*
Successfully completed	4 (23%)	4 (24%)	6 (35%)	14 (27%)
Terminated:				
Inadequate control of IOP	7 (41%)	7 (41%)	9 (53%)	23 (45%)
Terminated:				
Drug-related adverse experience	3 (18%)	1 (6%)	0 (0%)	4 (8%)
Discontinued.				
Not drug related	3 (18%)	5 (29%)	2 (12%)	10 (20%)
Total	17	17	16	50

As shown in Table 3, there were reports of clinically significant increases in cup/disc ratio ($\geq$0·2) and in progressive visual field loss in approximately one-half of the patients. The treatment groups were similar in this respect.

Overall, the mean changes in pupil size were less than +0·25 mm. Mean decreases in Schirmer tests were less than 2·5 mm. No changes were seen in the

Table 3 *Cup-disc ratio increases and visual field losses*

	0·5% Levobunolol	*1% Levobunolol*	*0·5% Timolol*
Cup-disc ratios increase$\leq$0·2	7 (44%)	9 (53%)	11 (65%)
Glaucomatous visual field losses*	6 (38%)	3 (18%)	10 (59%)

*Defined as Bjerrum's scotoma, nasal step, generalised construction, or enlarged blind spot not present at baseline examination

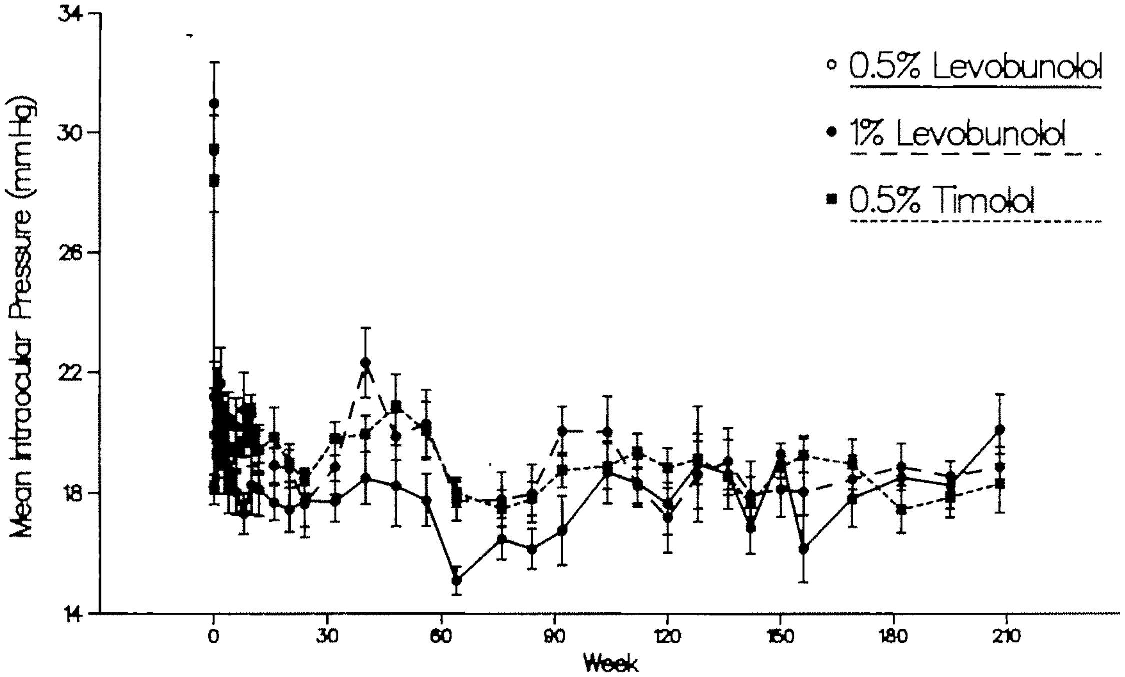

Fig. 2 *Significant decrease of mean IOP in each treatment group.*

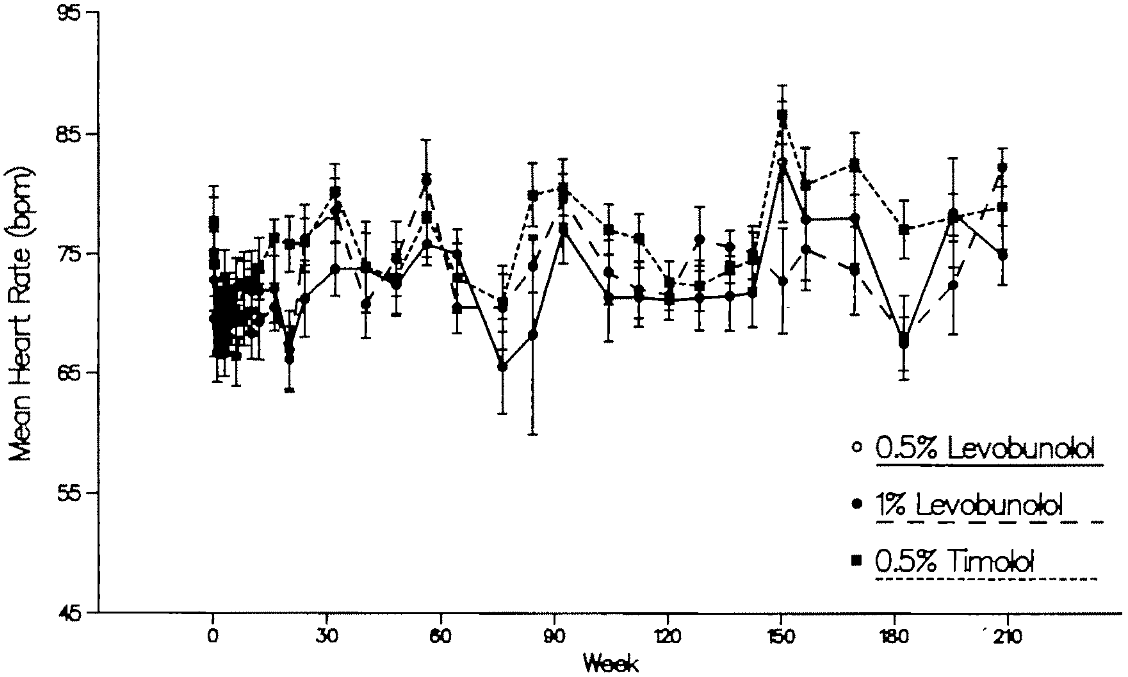

Fig. 3 *Mean heart rate decreased in first week of therapy, but decreases did not subsequently change.*

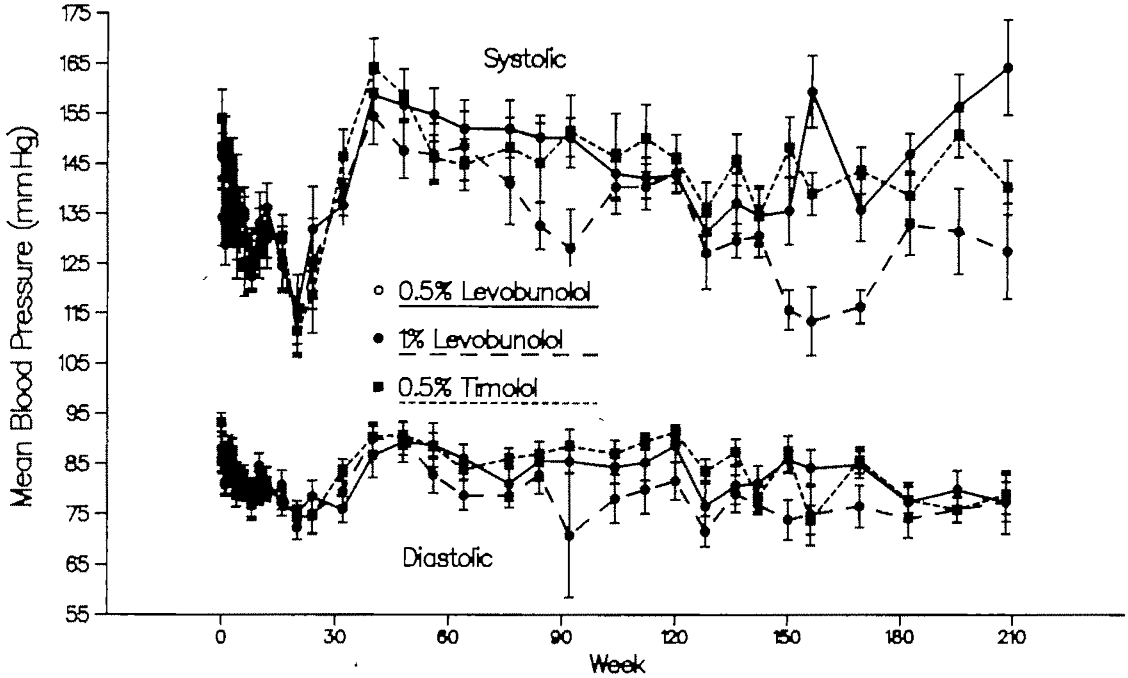

Fig. 4 *Decreases in mean systolic and diastolic blood pressure in each treatment group.*

blink test. None of these changes was of clinical or statistical significance.

While decreases in mean heart rate of 5–10 bpm were observed with the first week of therapy (Fig. 3), these decreases did not change significantly over time. There were decreases in mean systolic and diastolic blood pressure in all treatment groups (Fig. 4). There were no significant differences among groups in overall mean changes in heart rate or blood pressure (Table 4). In general, the incidence of clinically significant biomicroscopic and ophthalmoscopic findings were similar among the groups.

Patients' complaints were few, numbering only three. One patient using 0·5% timolol had epiphora at one visit. Another using 0·5% levobunolol reported unilateral trigeminal irritation, which resolved within one month. The third, who used 1% levobunolol, reported dizziness at three visits.

Table 4 *Overall mean changes in cardiovascular variables*

	0·5% Levobunolol	*1% Levobunolol*	*0·5% Timolol*
Heart rate (bpm)	−1·3	−3·9	−1·3
Systolic blood pressure (mmHg)	1·0	−5·0	−11·6
Diastolic blood pressure (mmHg)	−0·4	−3·9	−6·7

There were no significant differences among groups

Discussion

In this study levobunolol was as safe and effective as timolol for the long-term treatment of raised IOP. The long-term efficacy failure rate of approximately 15% per year was not only similar for levobunolol and timolol in this study but similar to that in a two-year study comparing the same treatments.[4] Interestingly, most of the efficacy failures occurred in the first two years. Outside the treatment protocol we found that these patients could be controlled with the addition of pilocarpine or dipivefrin. The long-term safety profile of levobunolol was good and similar to that of timolol. The possible untoward effects of levobunolol seen here, decreased cardiovascular function and topical allergy, are similar to those reported previously for both timolol and levobunolol.[4,7]

Of some concern in the present study is that, in spite of well maintained IOP reductions, some patients in each treatment group appeared to show additional visual field and nerve head deterioration. While manual Goldmann visual fields and subjective ophthalmoscopic estimations of cup-disc ratio are standard for clinical practice, they are quite variable.[8,9] Newer research techniques might have more objectively tracked these changes, if indeed they represent true glaucomatous progression.

However, as is well known, medical or surgical ocular hypotensive therapy may not necessarily halt the glaucomatous process. Some studies suggest that treatment retards the progression rate of glaucoma,[10,11] others do not.[12,13] Testing these hypotheses requires evaluation of a group of patients who receive no treatment and long-term follow-up with automated perimetry, as is being undertaken by Alexander and associates.[14] The present study was conducted not to answer the larger question of the efficacy of treatment on the disease itself but to compare a new ocular hypotensive agent, levobunolol, with a currently accepted one, timolol. In that regard we found both treatments equivalent.

As in other controlled studies, with neither levobunolol nor timolol did we see evidence of punctate keratitis, dry eye, corneal anaesthesia, or other ocular findings previously reported for timolol.[6,7] This suggests that such clinical reports may be relatively rare. Indeed, the frequency of ophthalmic examination in our study, 35 visits over four years, might tend to exaggerate the 'real' incidence.

Our four-year results support the trends we observed in the first year[1] as well as observations from other studies.[6] Levobunolol is as safe and effective as timolol for the long-term control of IOP in patients with glaucoma.

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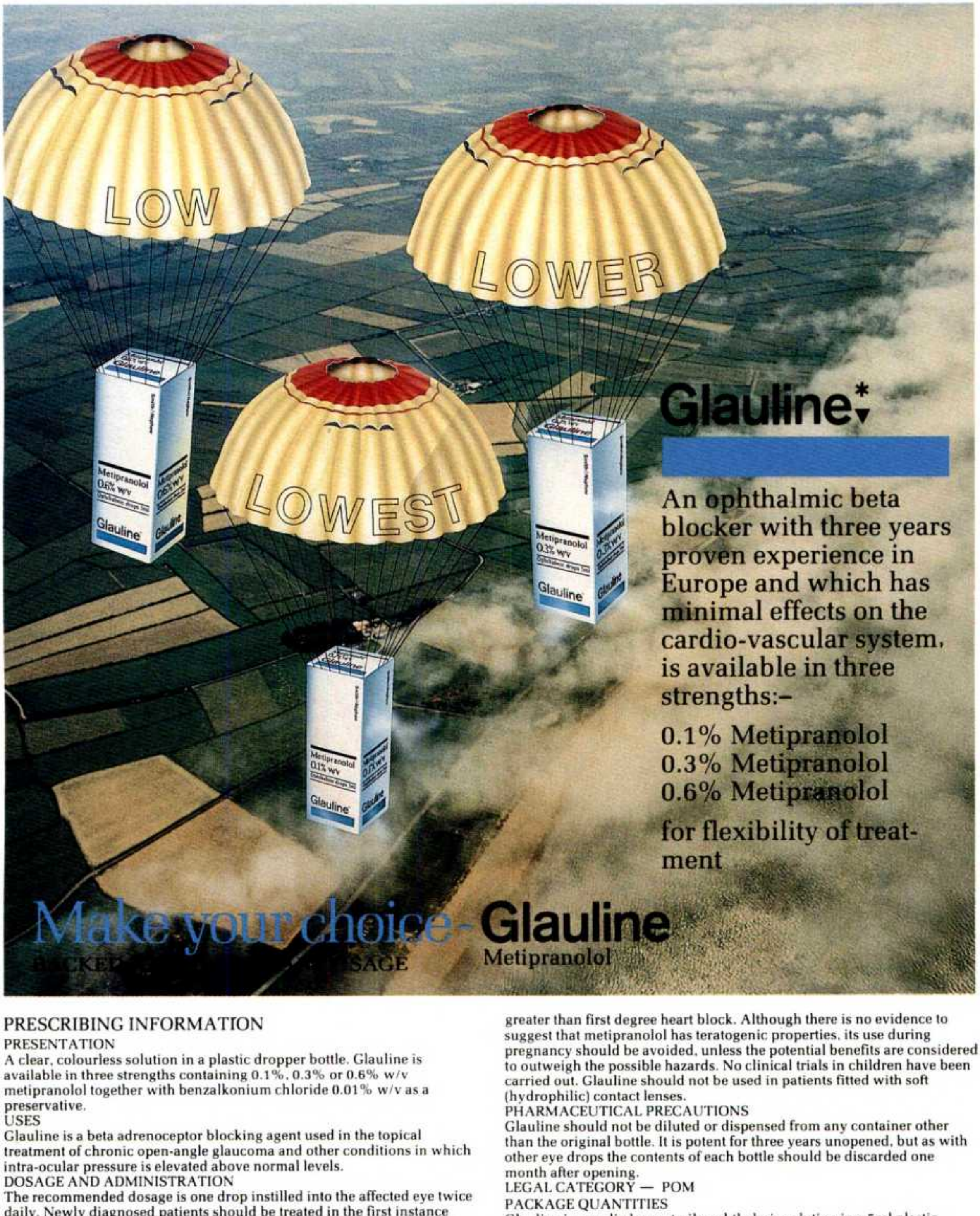

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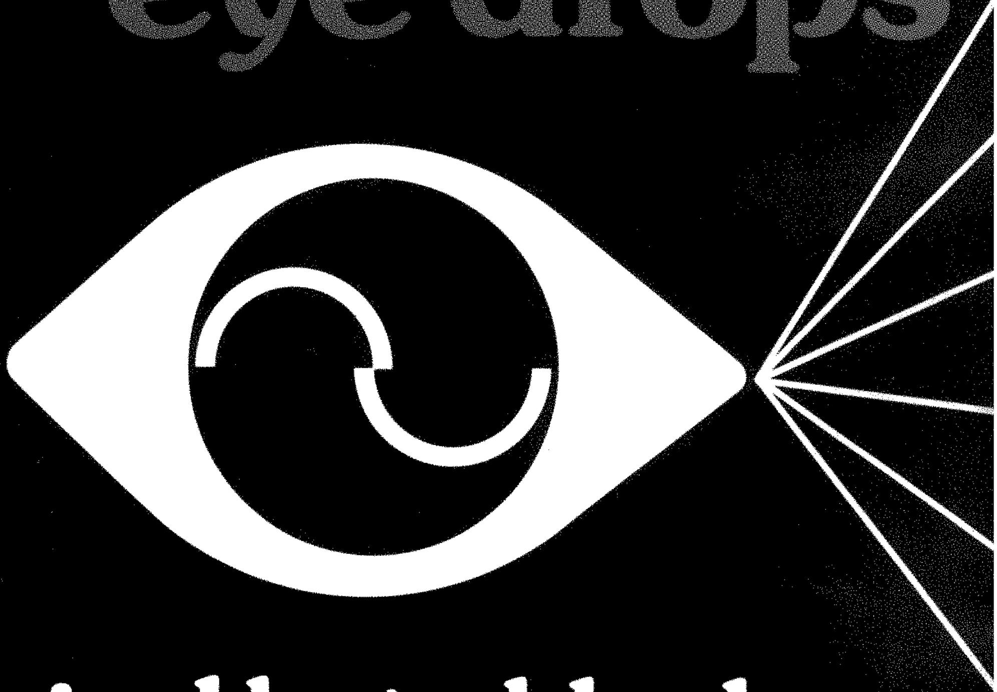

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British Journal of Ophthalmology, 1988, **72**, 897–899

Day-case cataract surgery

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From the [1]Birmingham and Midland Eye Hospital and the [2]Alexandra Hospital, Redditch

SUMMARY The results of a series of 40 cataract extractions with lens implantation performed on day-case patients under local anaesthesia are reported. The ways in which modern surgical techniques have rendered this a safe procedure are described, and the potential benefits of day-case intraocular surgery are discussed.

Day-case surgery is becoming increasingly widespread in Great Britain, and its cost effectiveness and popularity with patients are well established.[1] Though common in the United States, intraocular day-case surgery has not found universal favour in this country,[2] though a series of intracapsular cataract extractions without lens implantation has been reported.[3 4] The increased complication rate with intracapsular cataract extraction with overnight stay as compared to a five-day stay has been recorded.[5] In 1983 the Commission on the Provision of Surgical Services of the Royal College of Surgeons published its *Guidelines of day-case surgery*[6] and concluded that, in view of the necessity for supportive services, day-case surgery for intraocular procedures was unlikely to become widespread in the near future, and indeed these predictions were accurate.

We believe that using extracapsular surgery, however, and peribulbar as opposed to retrobulbar local anaesthesia, day-case cataract extraction is a safe procedure. In this report we describe a series of 40 cataract extractions without any problems attributable to day-case management. The importance of patient selection is stressed, as are the potential economies that the technique may bring.

Material and methods

Forty-one patients were selected as suitable for day-case surgery after inquiry into their home support and general physical and mental wellbeing. The procedure was explained to them as an alternative to our standard practice of overnight stay. All consented willingly, and keratometry and ultrasonic axial length measurement were carried out on them as outpatients. They were admitted at 11 am to the day unit of our hospital for afternoon surgery, signed their consent in the presence of the surgeon, and had any further questions answered.

One hour pre-operatively they were given 10 mg of temazepam orally, and one half-hour later the local anaesthetic was administered. This comprised topical 0·4% oxybuprocaine drops, and a peribulbar injection of 4–6 ml of 0·75% bupivacaine, injected through the lower eyelid into the peribulbar space but not entering the muscle cone. A Honan balloon was applied until surgery.

Patients who wore hearing aids were encouraged to retain them during surgery, and music was played if so desired. Drapes included the provision of a tent over the patient's mouth into which oxygen was piped.

All operations were performed by one of two surgeons, one of whom used a standard extracapsular technique, with removal of the anterior capsule prior to delivery of the nucleus, and the other an intercapsular technique, in which the nucleus was delivered through a horizontal cut in the anterior capsule and the anterior capsule removed after the insertion of the lens implant into the capsular bag. Both inserted capsular fixated lenses, of either a disc or Y-loop type. In two of the patients a lens was not inserted as a primary procedure owing to peroperative posterior capsule rupture. Sodium hyaluronate

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was used throughout to protect intraocular structures, but was removed just prior to full closure of the section, which was done using 9/0 or 10/0 nylon. A subconjunctival injection of ampicillin and Depo-Medrone (methylprednisolone) was given as well as two drops of timolol 0·5%. An eye pad and plastic cartella were applied. Patients were then taken back to the ward, whence they were collected by friends or relatives shortly after.

They all returned at 9 am the following day for their first dressing, at which time they were examined by the surgeon. All were given Maxitrol (neomycin, polymyxin B, dexamethasone) eye drops to take 2 hourly until their next clinic visit at between two and five days, when they again had a full ocular examination with tonometry. Subsequent visits were arranged as required, usually being at six weeks postoperatively, at which time they were referred to an optician for provision of spectacles.

Results

Forty cataract operations were performed in a group of 22 males and 19 females, with a mean age of 74·4 years, range 62–91. Twenty-six of the patients were in excellent general health, whereas the others suffered from the conditions shown in Table 1. All were able to lie still and flat during surgery. Their social circumstances varied, but all had either a relative or friend to stay with them over the first postoperative night except for one who lived in warden controlled accommodation and was closely supervised, and one for whom district nurse visiting was arranged.

Fourteen had had previous cataract surgery, but none as a day case. Only one patient required to be admitted overnight, and this was due to adverse weather preventing his collection from hospital. One patient was so anxious on admission that she decided to decline surgery and was discharged. She was subsequently offered an operation under general anaesthesia, but remained undecided as to whether to proceed.

None of the patients suffered any medical problems during their stay. In two patients no intraocular lens was inserted owing to posterior capsule rupture, though implantation as a secondary procedure is now planned. In neither did the surgeon consider that the use of day-case care had compromised the operation, and the anaesthesia had been effective.

There were two instances of a rise in intraocular pressure above 21 mmHg, to 24 mm and 27 mm respectively. These were transient and did not require treatment. There was no case of iris prolapse or endophthalmitis.

Patient satisfaction, though difficult to quantitate, was generally good. Only one patient regretted her decision to have day-case surgery rather than general anaesthesia, and six patients have requested surgery to their second eye on a similar basis.

Table 1 *Systemic illnesses suffered by day-case patients*

Illness	*No.*
Bronchitis/emphysema	3
Diabetes mellitus (oral control)	2
Previous cerebrovascular accident	2
Arthritis	3
Hypertension	6

Discussion

Much of the concern regarding day-case cataract surgery rests on the fear of raised intraocular pressure, iris prolapse, and endophthalmitis going unnoticed for a period of time. We believe that our techniques of anaesthesia and surgery minimise these problems, and in this series we have so far experienced none of them.

Posterior peribulbar anaesthesia, first described by Davis and Mandel,[7] though previously performed for many years, reduces the risks normally associated with retrobulbar anaesthesia. Because the anaesthetic is not injected within the muscle cone, the risk of damage is much lessened—in particular the risks of retrobulbar haemorrhage, optic nerve damage, perforation of the globe, and meningeal irritation or respiratory depression. It provides good analgesia and akinesia, and obviates the need for intravenous sedatives or neuroleptics and hence the need for the presence of an anaesthetist, though in all cases emergency anaesthetic cover was available.

Extracapsular cataract surgery with capsular fixated lenses, and removal of sodium hyaluronate prior to full wound closure reduces the incidence of postoperative pressure rises that others performing day-case or short-stay cataract surgery have experienced when using intracapsular surgery with chymotrypsin.[5] This, in combination with meticulous attention to wound closure, we believe is responsible for the lack of iris prolapse. In a number of patients in the series 9/0 rather than 10/0 nylon was used as suture material in order to provide added wound strength. With buried knots these did not prove uncomfortable to patients nor did they cause any astigmatic problems. This may be a more appropriate suture for day-case patients. Subconjunctival antibiotics were routinely used to minimise risks of infection.

Apart from patient preference the cost savings made by day-case surgery are significant. Precise estimates of the savings are difficult to formulate, since as long as facilities exist for inpatient management their disuse does not offer immediate savings. In our hospital we have fully utilised both the inpatient and outpatient day-case facilities, so the effect has been to reduce the waiting list rather than to effect immediate savings. Estimates of savings in the region of £270 have recently been suggested, however.

Day-case cataract surgery is not suitable for all patients, and selection is critical. We do not see the procedure as a replacement for conventional inpatient management but rather as an adjunct to it. Particularly in times of ever increasing demands on Health Service funds, intraocular day-case surgery helps to make the best of resources.

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Argon laser treatment of lipid keratopathy

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SUMMARY Sixty-three cases of vascularised lipid keratopathy were treated with the argon laser to occlude feeder vessels which had been identified by fluorescein angiography. There was a reduction in extent in 62% and density in 49%. Visual acuity was improved in 48%. Six patients had keratoplasties shortly after treatment, none of which showed graft rejection. Minor complications included temporary haemorrhage into the cornea and iris atrophy. A more serious problem was severe corneal thinning after resorption of lipid. The patients had to be carefully followed up and maintained on a low dose of topical steroid.

Most lipid keratopathy is secondary to corneal inflammatory disease and is vascularised. The commonest causes are herpes simplex and herpes zoster disciform keratitis. Treatment involves firstly controlling the primary inflammatory disease and then the lipid deposits. Many attempts have been made to occlude the blood vessels supplying these deposits[1-9] in the hope that further lipid deposition can be prevented, some resorption occur, and, in some cases, the host made safer for grafting. More recently the argon laser has been used for this purpose.[10-13] I was pleased with our preliminary results[13] but was struck by the extensive iris atrophy induced. The use of the Abraham contact lens has minimised this problem.[14] The histopathology of treated corneas has been recorded and a mechanism of vascular closure proposed.[15] This paper presents my results from 1975 onwards with a minimum follow-up of one year.

Material and methods

Patients with lipid keratopathy were referred for assessment and treatment from many centres, the chief of which were Moorfields and the Western Ophthalmic Hospitals. The history was recorded on a score sheet, including the suspected aetiology of the keratitis, duration, and therapy. Slit-lamp examination concentrated not only on the extent, density, and vascularity of the lipid deposit but also on the iris and lens appearance. A note was added to the score sheet on the shape and position of the deposits—whether they were central or eccentric disciform, marginal, diffuse interstitial, or deep, and a drawing was made. A random number of patients had their fasting blood lipid profile assessed, which included serum concentrations of cholesterol, triglyceride, betalipoprotein, prebetalipoprotein, and chylomicra.

Colour photographs of the whole cornea (with a dilated pupil) were taken on a Zeiss photo slit-lamp at ×2 film magnification with identical settings, lighting conditions, and film (Kodak Ektachrome 200). A careful grading was made on the density and extent of the lipid by means of a Zeiss Dokumator to project the transparency on its built-in screen over which a transparent grid was superimposed to encompass the whole cornea and divided into 100 squares. Extent was calculated from the number of grid squares involved (including those that were more than half filled) and expressed as a percentage of the whole cornea. Density was classified into four categories based on the degree of masking of underlying structures: 0=transparent, 1=slight blurring of iris crypts, 2=iris colour only appreciated, 3=pupil vaguely discerned with full illumination, and 4=total opalescence with dense creamy yellow lipid. Fluorescein angiography was carried out in all new cases with the modified Zeiss photo slit-lamp, 20% fluorescein, and video by the techniques described before.[15] The 35 mm film was examined and the vascularity classified as slight (1), moderate (2), and profuse (3), while the vascular stems at the limbus were defined as single and narrow or multiple and diffuse. The video was analysed to establish the dynamic filling pattern of the vessels. These details were added to the diagram and score sheet.

Treatment was carried out with a coherent argon

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laser 900 series via the Abraham contact lens as described previously.[14] In most cases it was possible to achieve initial vessels closure in one treatment session, but in cases with dense vascularisation it was best to treat three times in one day and to re-examine a few days later with a view to further lasering. Immediately after treatment prednisolone 0·3% drops were administered twice a day until the next visit. A month was usually adequate for the first follow-up visit and then three or six monthly depending on the success of vessel closure. At each follow-up examination the density, extent, and vascularity of the deposits were reassessed and colour photographs repeated, but angiography was carried out only in doubtful cases. Any remaining vessels were again treated by the laser. All relevant details were entered in the score sheet. The attempt was made to withdraw the prednisolone drops, entirely but cautiously, over one year, but they had to be used after lasering and if there was any sign of active keratitis. The intraocular pressures were regularly checked while the patients were taking steroids, and in case of raised intraocular pressure fluoromethalone drops were substituted. Where lipid deposits were very dense and central the patients received grafts as soon as vascular flow had been stopped.

Results

Sixty-three patients were reviewed with a minimum follow-up of 12 months. The sex distribution was equal and the average age was 52. Table 1 depicts the morphology and aetiology of the cases. Two of these cases were old corneal grafts with marginal lipid deposits at the graft-host junction and the bacterial infection was related to contact lens wear.

Thirty-nine cases (62%) showed a reduction in the extent of the lipid, 13 (21%), no change and 11 (17%) an increase. If the patients were divided into two groups, one with lipid involving less than 20% of the cornea and the other with more than 20%, there was a highly significant improvement after treatment (Table 2). The density of deposits was reduced in 31 (49%), the same in 26 (41%), and worse in six (10%). Dividing the patients into two groups again, one with density of lipid of 3 units or more and the other 2 units or less, showed a significant reduction in density after treatment, particularly in the second group (Table 3). There was improvement in both extent and density in 23 cases (36%) (Figs. 1, 2, 3). Snellen visual acuity was improved in 30 cases (48%), unchanged in 19 (30%), and worse in 14 (22%). However if the patients were divided into two groups, one with vision of 6/18 or worse and the other with 6/12 or better, there was a small but non-significant improvement in both groups (Table 4). Combined improvement in all three aspects occurred in 14 cases (22%) apart from those cases that were grafted (Fig. 4). We compared the number of burns per degree of vascularity and per mm² of corneal opacity, but there were no enough cases in the former measurement to give a significant result, and the latter was equivocal (Table 5).

Six grafts were carried out after treatment by laser, four of which were elective and two carried out urgently because of descemetocele formation. Two of these six required regrafting, one because of poor

Table 1 *Aetiology and morphology of lipid keratopathy*

Aetiology	*Central disciform*	*Eccentric disciform*	*Marginal*	*Diffuse interstitial*	*Diffuse deep*
Herpes simplex	13	14	3	5	0
Herpes zoster	5	14	2	0	0
Acne rosacea	0	0	1	0	0
Bacterial	0	1	0	0	0
Unknown	0	2	1	0	2

Table 2 *Effect of laser on the extent of opacity (expressed as a percentage of the corneal surface)*

	More than 20%	*Less than 20%*
Before treatment	36 (57%)	27 (43%)
After treatment	18 (29%)	45 (71%)

$\chi^2=9{\cdot}36$ $p<0{\cdot}01$, highly significant.

Table 3 *Effect of treatment on the density of opacities*

	3 Units or more	*2 Units or below*
Before treatment	35 (56%)	28 (44%)
After treatment	22 (35%)	41 (65%)

$\chi^2=4{\cdot}61$. $p<0{\cdot}05$, significant.

Table 4 *Effect of laser treatment on visual acuity*

	6/18 or worse	*6/12 or better*
Before treatment	42 (66%)	21 (34%)
After treatment	34 (54%)	29 (46%)

$\chi^2=1{\cdot}66$. p Non-significant

Table 5 *Effect of intensity of treatment*

Number of burns per mm² of opaque cornea	*Better*	*Worse*
Below 75/mm²	47 (75%)	16 (25%)
Above 75% mm²	37 (58%)	26 (42%)

$\chi^2=1{\cdot}56$. p about 0·1 If 1 in 10 is the criterion of significance, this is significant.

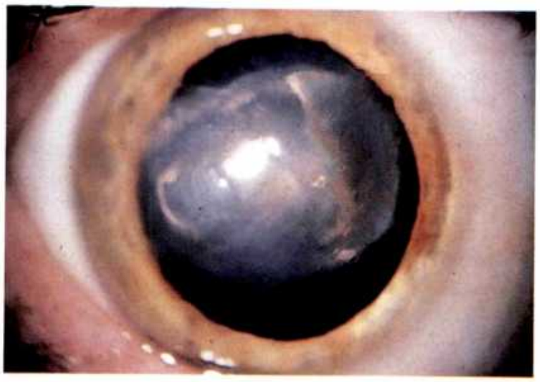

Fig. 1A *Herpes simplex disciform scarring.*

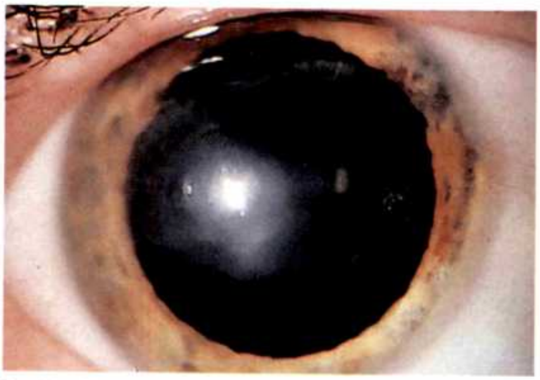

Fig. 1B *Same case two years after treatment.*

donor endothelium and the other because of recurrence of herpes simplex keratitis spreading into the donor cornea. All were clear after a minimum follow-up of 36 months.

The most spectacular result was in a woman with an old herpes simplex diffuse interstitial keratitis, vision of hand movements, lipid density three, extending over the entire cornea, vascularity four with multiple stems. She received 13 000 burns in 18 treatment sessions over five years. Now eight years later her visual acuity is 6/36, lipid density is 1, extent 0·3, and the great majority of the vessels have been closed (Fig. 3). It is interesting that despite extensive iris atrophy there is no sign of lens opacities or retinal damage.

It was possible to close all the blood vessels at the end of a treatment session. However, in cases of very vascular keratopathy there was a tendency for some vascular channels to reopen soon afterwards, but eventually, after repeated treatment, all but some very small vessels with very slow flow were successfully closed.

The commonest immediate complication is haemorrhage around the treated vessels, which rarely spreads widely between corneal lamellae. However, this is a temporary phenomenon and, though a little disturbing to the patient, always resorbs. Less commonly there is temporary peaking of the pupil in the sector underlying that treated with the laser. Patients who had multiple laser treatments all developed some degree of iris atrophy underlying the treatment zone. There was occasional reactivation of keratitis, but all except one responded well to increasing topical steroids (with antiviral cover when appropriate). The exception was a patient who did not take his drops and failed to attend follow-up for over a month, in whom a marked stromal swelling with cellular infiltration and increase in opacity resulted. Two cases of dense disciform lipid deposits developed rapid central stromal thinning within one month of treatment, culminating in the development of descemetoceles at four and six months respectively. Both received grafts shortly afterwards and have remained clear over a follow-up period exceeding two years. All cases of disciform keratopathy that responded successfully to treatment showed some

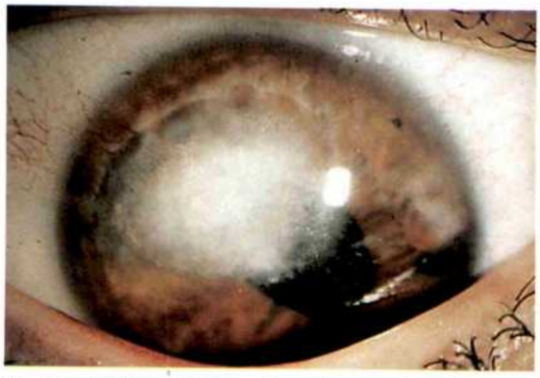

Fig. 2A *Old bacterial keratitis with eccentric disciform scar.*

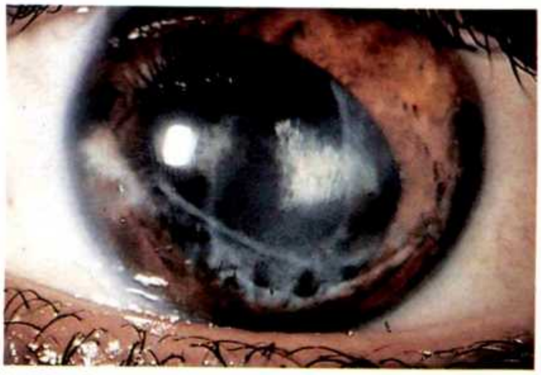

Fig. 2B *Same case three years after treatment.*

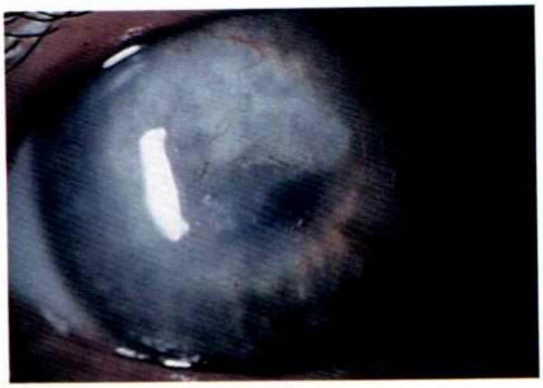

Fig. 3A *Old diffuse scarring from herpes simplex.*

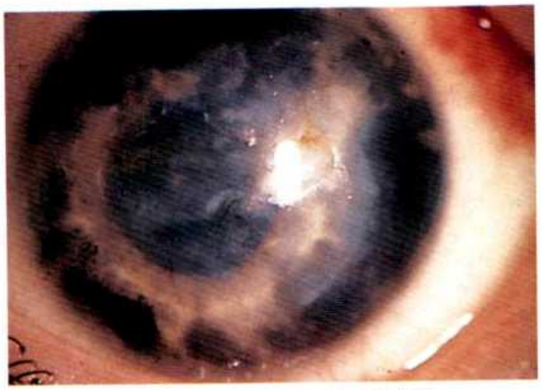

Fig. 3B *Same case four years later after 13 000 burns.*

degree of stromal thinning. Two patients developed open-angle glaucoma and appreciable field loss due to a combination of chronic keratouveitis and topical steroids. I am not aware of any lens or retinal damage as a result of the therapy.

Fourteen randomly selected patients had their fasting blood lipid profile assayed. Nine of these were normal, four had hyperlipoproteinaemia (two Fredrickson's type 2A and 2 Fredrickson's type 2B).

Discussion

The results of argon laser treatment of lipid keratopathy are encouraging, but clearing of the lipid is slow and may take several years to be apparent. Even though Snellen tested visual acuity improved in only 30 cases, many other patients noted an improvement in photophobia and quality of sight. It is important to stress that the usual natural history of a vascularised lipid keratopathy is to advance with deterioration of vision, so that arresting the condition is a significant achievement. The results of grafting treated cases were excellent, and a number of other successful cases were not included in this series because of inadequate personal follow-up. It seemed best to arrange for laser treatment three days prior to grafting under topical steroid cover, which rendered the cornea avascular at surgery and precluded descemetocele formation.

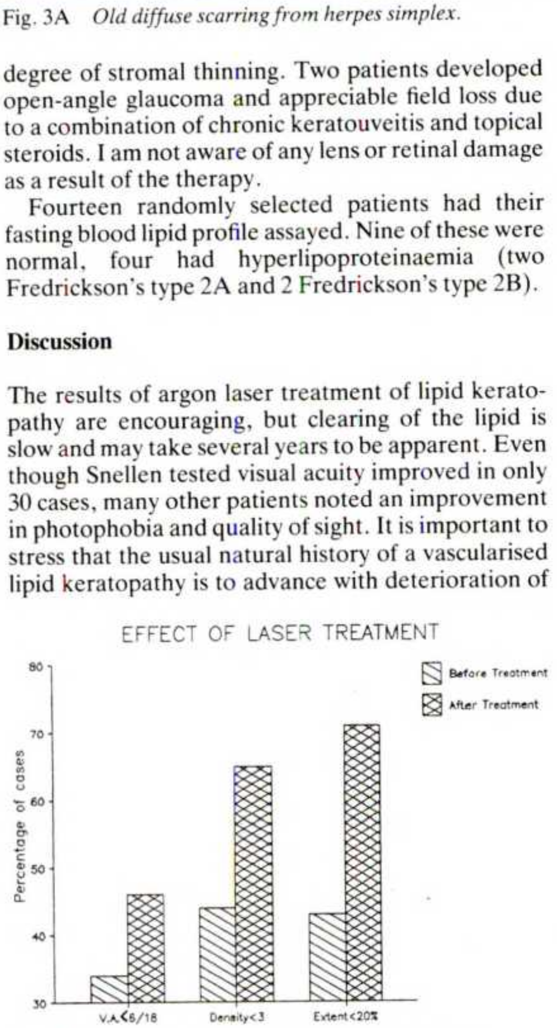

Fig. 4 *The effect of laser treatment on visual acuity (expressed as those cases better than 6/18), lipid density (those cases less than 3), and extent (those cases less than 20% of the cornea).*

Patients on the whole tolerated the treatment very well. The Abraham lens not only made the application of the burns more accurate but also kept the eye steady. The main complaint from patients was that the laser beam dazzled their other eye (it was worth covering it with the operator's hand during firing). It should be admitted that prolonged treatment sessions were also uncomfortable for the surgeon and that on the rare occasions when fluorescein angiography had been carried out just previously the dazzle was even more bothersome. The importance of using the postoperative drops was stressed to the patients, and regular applanation was important.

The video corneal angiograms proved very useful for identifying feeder vessels and flow. They also clearly showed that many of the eccentric disciform keratopathies and all the marginal and half of the idiopathic deep keratopathies had marked ischaemic changes in neighbouring episclera. The first two types were usually caused by herpes zoster and probably at the time of the preceding acute keratitis had an ischaemic episcleritis.

The mechanism of lipid clearance is uncertain but is probably due to ingestion by macrophages wandering between corneal lamellae which then migrate to the limbus, whence they gain access to lymph and blood vessels. Successful closure of vessels will obviously prevent further deposition of lipid. Another factor is the obvious disruption in the corneal tissues caused by the laser burns, which may facilitate diffusion of lipid away from the keratopathy. As expected, fibrous scarring of the corneal stroma did not clear. Thinning occurred as the lipid 'leached out', implying that the lipid deposits had artificially contributed to corneal thickness and in fact revealed how much corneal stroma had been destroyed by the pre-existing keratitis.

Prevention of the lipid keratopathy is an important element in any discussion on treatment. Probably all patients should have their fasting blood lipid profile assessed and any lipid abnormality appropriately corrected. (Although no data are available on the effect of hyperlipidaemia on the development of secondary lipid keratopathy in humans, there is in rabbits.[16]) More importantly, a vascularising active keratitis, particularly due to herpes zoster, should be adequately treated with topical steroid to prevent excessive scarring.[17-19]

I thank my colleagues for referring their patients, Professor R F Fisher of the Western Ophthalmic Hospital for his statistical advice, Miss S Ford for her invaluable help with the photography, and Coherent Lasers for helping finance the colour photographs.

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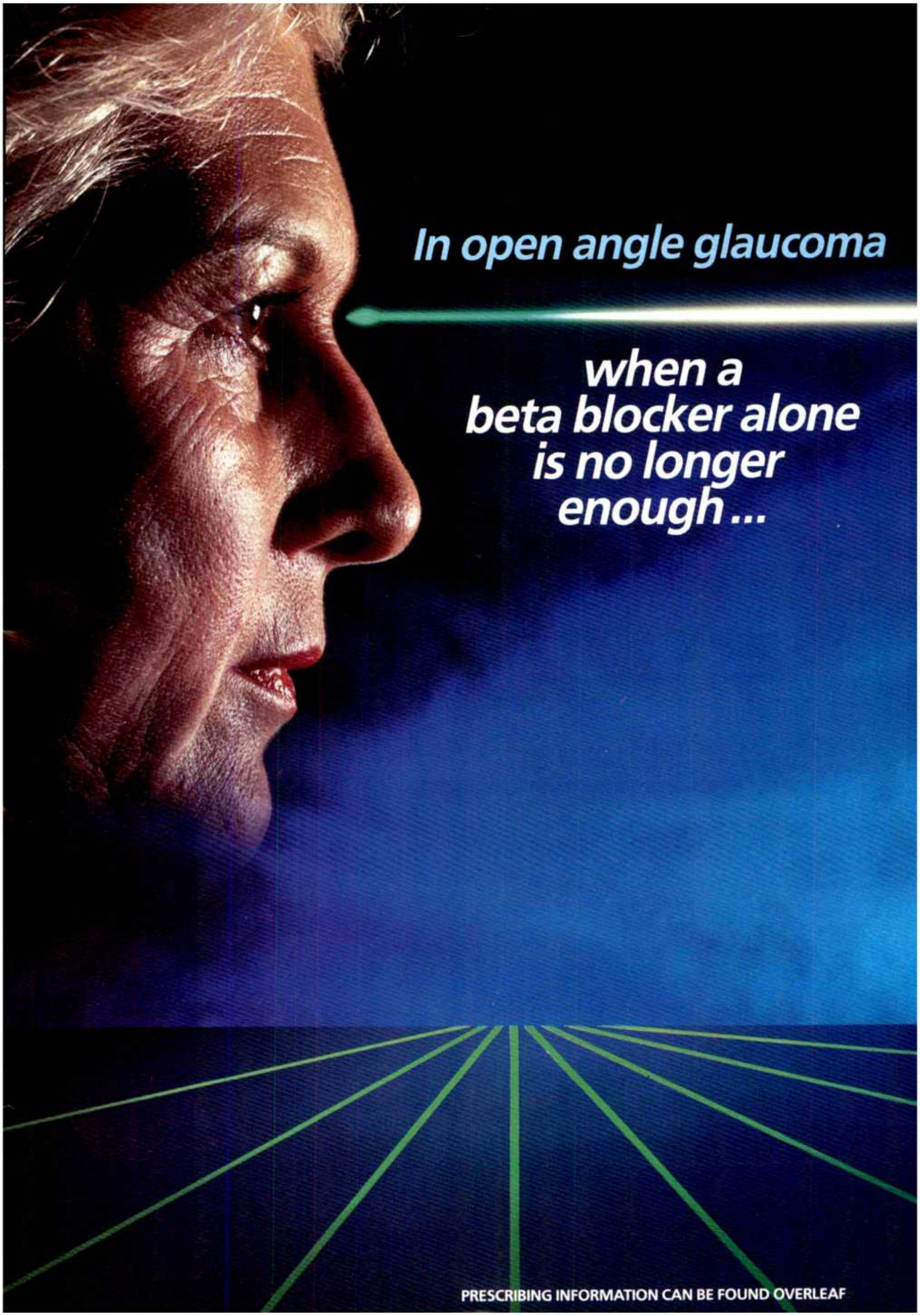
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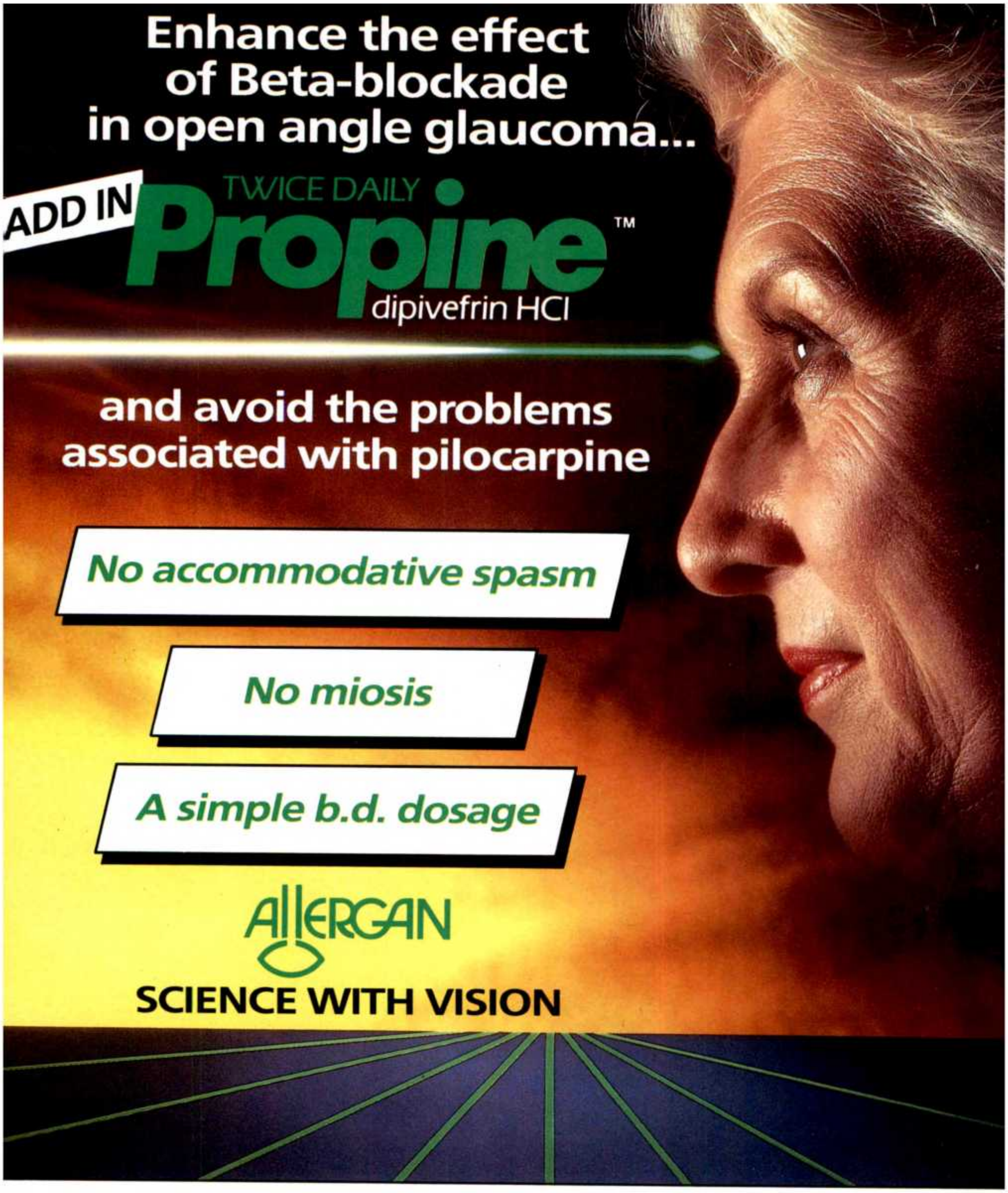

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Intraocular lymphoma: immunological and cytological analysis

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SUMMARY We retrospectively reviewed the cytology and immunohistology of vitreous specimens from nine patients with intraocular lymphoma (ocular reticulum cell sarcoma). A single vitreous biopsy specimen was not always adequate to establish the diagnosis in this condition. Cytological evaluation was more accurate than lymphocyte surface marker analysis to differentiate lymphoma from uveitis. The immunological features of these tumours indicate a heterogeneous group of intraocular lymphomas.

Ocular reticulum cell sarcoma is a rare lymphoma which most commonly involves the uvea, retina, vitreous, and central nervous system.[1] Patients present with painless loss of vision; less commonly other eye symptoms, simultaneous eye and brain symptoms, or neurological manifestations alone can herald disease onset.[1-4] While some patients initially present with unilateral eye disease, over 75% of cases develop bilateral tumours. Central nervous system involvement has been reported in approximately 75% of cases and is the usual cause of death.[1 2 7 8]

Approximately 65 cases of ocular reticulum cell sarcoma have been reported. Recent data has shown that this diagnostic term is a misnomer, but its use is ingrained in the ophthalmic literature.[1] The initial term for this non-Hodgkin's lymphoma was reticulum cell sarcoma.[9] Rappaport reclassified these large cell tumours as histiocytic lymphomas.[10] Most non-Hodgkin's lymphomas of the CNS are of B-cell derivation.[11 12] A few patients have been reported in whom immunological surface marker techniques have shown that the vitreous cells consist of B-cell and occasionally null cell lymphomas.[13-15] These malignant cells are probably derived from lymphocytes or their progenitors and not histiocytic cells. Most investigators classify these tumours as diffuse large cell lymphomas, which are quite heterogeneous.[16]

The correct diagnosis of intraocular lymphoma is often not established until late in the disease course. Most patients are initially misdiagnosed as having an idiopathic diffuse uveitis, posterior uveitis, or vitritis. Even when there are yellowish white chorioretinal lesions and vitritis, an almost pathognomonic presentation, diagnosis is usually delayed.

The sensitivity and specificity of diagnostic tests in the evaluation of these patients is unclear. Cytological evaluation has been the benchmark for diagnosis. Since these tumours may be monoclonal, some investigators have suggested that immunological marker studies might improve diagnostic accuracy. We have retrospectively analysed nine cases in which cytological and immunological data were available to determine the accuracy of these techniques.

Materials and methods

All patients were referred to the University of California, San Francisco, evaluated by one of us (DHC), and the diagnosis of an intraocular lymphoma was made. A complete physical examination, bone marrow biopsies, body and brain computed tomographic (CT) scans with contrast, complete blood counts, cerebrospinal fluid cytology,

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and vitreous aspiration for immunological and cytological evaluation were performed on all patients. In those patients with minimal vitreous involvement and good vision a pars plana aspirate with a 20 gauge needle was used to obtain a vitreous specimen. (Two cases, 1 and 2, both later had core vitrectomies.) Patients with more extensive involvement had an initial core vitrectomy performed. In the latter group of patients an infusion port was sutured in place, and a 20 gauge needle was used to make incisions for a light pipe and a vitrectomy instrument. Prior to placing the vitrectomy instrument in the eye, approximately 1 ml of liquid vitreous was aspirated with a 20 gauge blunt needle. No complications were noted as a result of this aspirate. The specimen was divided in two parts and taken from the operating room to the laboratory for immediate cytological and immunological analysis. In three cases a separate, second sample was simultaneously analysed; this was obtained through the vitrectomy instrument and harvested from the balanced salt solution plus-specimen reservoir.

The processing of specimens for cytological analysis was performed in a standard manner.[17 18] The specimen was processed through a 5 μm Millipore filter under negative pressure. It was then fixed in 95% ethanol overnight, and stained using a modified Papanicolaou technique. Cytological features were independently analysed in a masked manner by two cytopathologists. Parameters studied included overall cellularity, cell size, presence of necrotic debris, polymorphonuclear leucocytes, mitotic figures, nucleoli, the degree of nuclear membrane and chromatin irregularity, and the proportion of abnormal cells.

The processing of specimens for immunological study has previously been described[19] Briefly, vitreous lymphocytes were analysed on a fluorescence activated cell sorter (FACS IV, Becton Dickinson Co., Sunnyvale, CA) Peripheral blood lymphocytes were purified by Ficoll-hypaque gradient centrifugation Vitreous samples were filtered through nylon mesh before analysis. Samples of vitreous, and blood lymphocytes were distributed in seven bovine serum albumin coated Eppendorf microtubes (Beckman Instruments, Inc., Irvine, CA). Cells were washed, labelled, and fixed as previously described[20] Analysis was performed with a dual channel, two colour FACS IV. Fluorescein isothyocyanate or phycoerythrin conjugated monoclonal antibodies (a gift from Becton-Dickinson) were used. Antibodies were selected to react with T cytotoxic/suppressor cells (Leu 2a), T helper/inducer cells (Leu 3a), total T cells (Leu 4), total B cells (Leu 16), T suppressor cells, large granular lymphocytes, and natural killer cells (Leu 11), and activated T cells (DR and IL-2). Not all antibodies were used in all cases, and in three patients studied more than four years ago the analysis was performed with fluorescence microscopy for surface immunoglobulin, kappa and lambda light chains to delineate B-cells, and sheep red cell rosette formation to assess the number of T-cells.

Results

Nine patients with intraocular lymphoma for whom both immunological and cytological data was available were included in this study. The clinical and computed tomographic data are summarised in Table 1. The age range was from 35 to 82 with a mean of 60·6 years. Four patients (cases 1, 3, 6, 8) had

Table 1 *Clinical and CT data*

Case	*Age/race sex*	*Interval SX/DX (months)*	*Vitreous cells*	*AC cells*	*CNS symptoms*	*CT scan*	*Chorioretinal lesions*
1	72/WM	3	OS 2+	0	Confusion, ataxia poor memory	Density R lateral ventricle	Chorioretinal lesions discrete with detachment and retinal haemorrhage
2	72/WF	4	OD 2+, OS 3+	0	None	Negative	Exudative detachment
3	82/WF	0	OD 2+, OS rare	OD 1+, OS 1+	Atypical Parkinsonism (1983)	Negative	Negative
4	73/WF	3	OD 2+, OS 4+	0	None	Negative	Negative
5	51/WM	1	OD 3+, OS 4+	0	None	Negative	Discrete choroidal infiltrate
6	35/WF	4	OS 4+	OS 4+	Severe progressive peripheral neuropathy	Negative	Unable to visualise fundus
7	53/WM	1	OD 3+	OD 2+	None	Orbit only	Retinal and choroidal infiltrates
8	62/WM	27	OU 3+	OD 1+	Weakness in shoulders	Frontal lobe	Retinal and choroidal infiltrates
9	49/WM	0	OD 3+, OS 4+	OS 1+ rare OD	None	L internal capsule	Retinal and choroidal infiltrates

OD=right eye, OS=left eye, OU=both eyes 2+=10–20 cells, 3+=20–30 cells, 4+=too numerous to count.
W=White SX/DX=Onset of symptoms to start of treatment. AC=anterior chamber

symptoms of the central nervous system prior to the discovery of ocular disease; one of these patients had the diagnosis of a cerebral lymphoma confirmed before the development of ocular disease. The interval between first ocular or nervous system symptoms and eye diagnosis was 0 to 27 months. Brain CT with contrast using second through fourth generation scanners showed brain lesions in three cases; two patients had magnetic resonance image scans which mirrored the pathology noted on CT brain scan.

Ocular examination showed vitreous cells in all patients at the time of diagnosis. Four patients had minimal or absent anterior chamber cells. Chorioretinal lesions were noted in five cases, and one patient's media opacities were too dense to ascertain fundus detail. The retinal and choroidal lesions were sometimes discrete, with areas of retinal pigmentary hyperplasia, and were occasionally diffuse and creamy in nature (Fig. 1). Exudative retinal detachment and intraretinal haemorrhage were noted along with discrete chorioretinal lesions in one patient.

Follow-up and treatment data are summarised in Table 2. The follow-up in these patients ranged from two months to nine years (mean 3·2 years, median 11 months). Six patients received eye and brain radiation. Five received intrathecal chemotherapy. Three patients received only ocular and brain radiation. Two patients died; one death occurred during treatment and one 31 months later.

Table 2 *Treatment and survival data*

	Treatment	*Survival*	*Time from diagnosis to last follow-up (months)*
1	Radiotherapy eye and brain. Died before end of therapy	Dead	1
2	Radiotherapy eyes and brain. Intrathecal chemotherapy	Alive	5
3	Radiotherapy eyes only	Alive	6
4	Radiotherapy eyes and brain	Alive	13
5	Radiotherapy eyes and brain	Alive	29
6	Radiotherapy (30 Gy) eyes and brain. Intrathecal mtx	Alive	14
7	Radiotherapy (50 Gy), eyes only	Alive	95
8	Radiotherapy (40 Gy), eyes and brain. Intrathecal and systemic chemotherapy	Dead	31
9	Radiotherapy (45 Gy), eyes only. Intrathecal and systemic chemotherapy	Alive	102

mtx=Methotrexate.

In all cases the two cytopathologists independently agreed on the diagnosis of intraocular lymphoma. On examination of the vitreous biopsy slides four cytological features were characteristic and necessary to establish the diagnosis of intraocular lymphoma: irregular nuclear contours, lobation of nuclei, coarse irregular chromatin, and presence of nucleoli (Fig. 2). Mitoses were occasionally observed in intraocular lymphoma specimens, and necrotic material was sometimes present (Fig. 3). When inflammatory cells were present in intraocular lymphoma specimens, they were not numerous.

In two patients with symmetrical disease, the diagnosis could not be made either prospectively or retrospectively on the initial vitreous biopsy. In one of these cases two separate biopsies were performed on the first eye (an initial diagnostic procedure followed several months later by a therapeutic vitrectomy), with only inflammatory cells noted on both occasions. The immunopathological pattern was polyclonal in both biopsies. A third vitreous biopsy at a later date established the diagnosis; retrospective analysis of the two earlier specimens was negative for malignancy. In the second case,

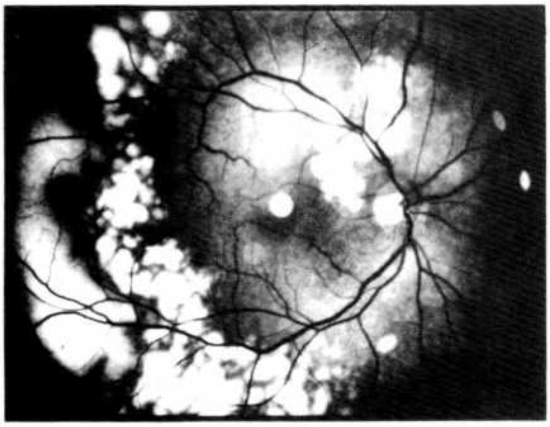
Fig. 1 *Clinical photograph of intraocular lymphoma with chorioretinal infiltrates.*

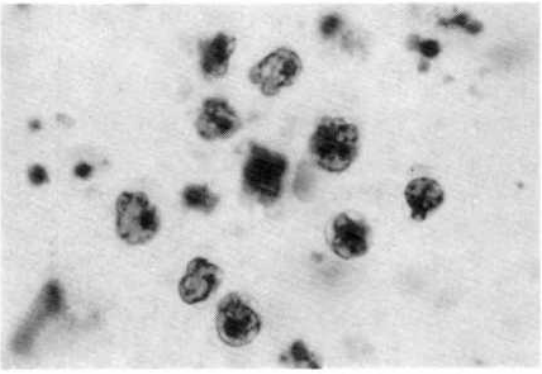
Fig. 2 *Vitreous sample from case 8 showing prominent nucleoli, coarse chromatin, and irregular nuclear membranes including focal lobation.*

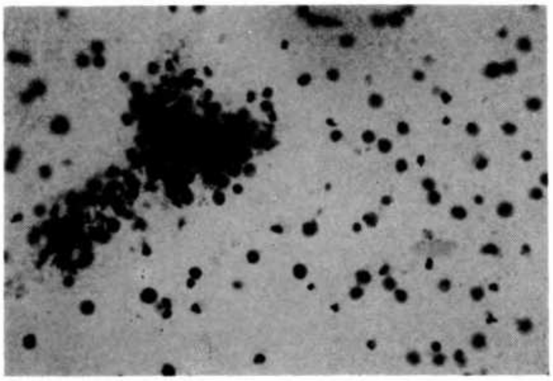

Fig. 3 *Vitreous sample from case 2 showing high cellularity and focal necrotic debris intermingled in a cluster of lymphoma cells.*

because of strong clinical suspicion and an equivocal cerebrospinal fluid cytology, the contralateral vitreous was removed one week later and a cytological diagnosis of intraocular lymphoma was established.

A number of independent cytological parameters were assessed in a masked manner. In most of them the agreement between the two cytopathologists was quite good. As an example, the R value for the assessment of general cellular background was 0·936. Similarly, agreement between the two observers was excellent in delineating the number of mitotic figures, irregularity of nuclear contour, and chromatin pattern. The estimation of percentage of abnormal cells and number of polymorphonuclear cells showed less agreement among the two readers, with R values ranging between 0·1 to 0·4. These latter two parameters tend to be focal cytological findings, and discrepancies between independent observers might be due to review of different areas of the slides. Fortunately, neither percentage of abnormal cells nor the number of polymorphonuclear cells are used to establish the cytological diagnosis of intraocular lymphoma. In no case was there disagreement on the diagnosis of lymphoma.

In three cases we compared vitreous cytological detail in specimens removed directly from the eye with a 20 gauge needle versus material taken through the vitrectomy unit and obtained from the aspiration reservoir. Figs. 4 and 5 demonstrate the loss of cellular detail which occurred when the specimen was obtained through vitrectomy instrumentation. The relative contribution of the action of the vitrectomy instrument versus maintaining the cells for 30–60 minutes in BSS plus is not clear.

Immunological assessment of cell type was performed on multiple specimens from the nine cases studied (Table 3). Six specimens were not typeable with the reagents used, and defined as null cell lymphomas (Table 3). Two specimens were polyclonal, and two consisted of probable T-cell neoplasms. Using these conventional monoclonal anti-T cell, anti-B cell, anti-natural killer cell, and anti-macrophage antibodies, we could demonstrate probable monoclonality in only two of nine cases.

Discussion

Ocular reticulum cell sarcoma is a lymphoma with an unusual predilection for the eye and central nervous system.[1] Unfortunately, because of both its rarity and

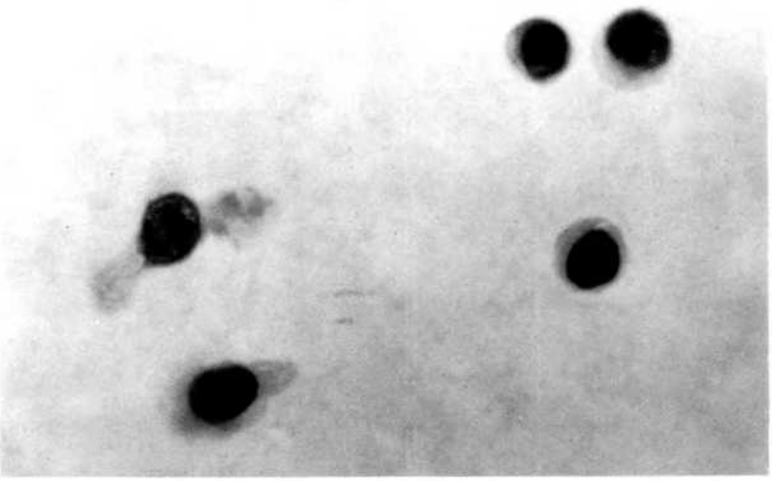

Fig. 4 *Vitreous specimen obtained directly with 20 gauge needle and syringe.*

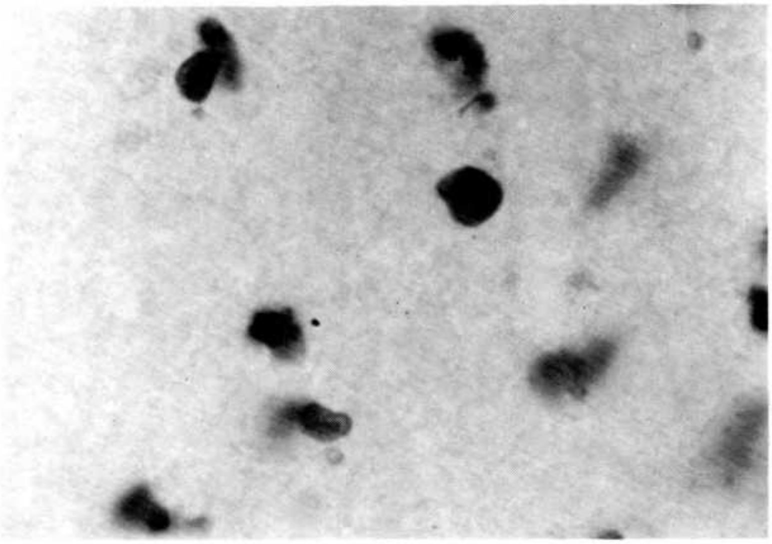

Fig. 5 *Vitreous specimen from same case as Fig. 4 obtained through vitrectomy instrument. Note loss of cellular detail.*

diagnostic difficulties, its differentiation from uveitis is difficult and often delayed. We have retrospectively reviewed nine cases of intraocular lymphoma in which both immunological and cytological analyses were performed. Three important conclusions can be drawn from this study. First, we have observed that cytological evaluation is more accurate than lymphocyte subset analysis in the diagnosis of these cases. Secondly, a single vitreous biopsy was not always adequate to establish a diagnosis. Thirdly, there appeared to be cellular degradation when specimens were obtained with vitrectomy and aspiration rather than biopsy with a syringe and needle.

As shown in Table 3, we observed lymphocyte heterogeneity on immunological analysis of lymphocyte surface markers in at least six cases. This finding

Table 3 *Immunological surface marker studies*

	Vitreous cytology	*Intraocular cell typing*						
		Leu2+	*Leu3+*	*Leu4+*	*Leu11+*	*Leu16+*	*DR+*	*IL2+*
1	Lymphoma	1%	2%	2% (Null cells)	<1%	1%	1%	<1%
2	OS: non-diagnostic	19%	16%	32% (Polyclonal)	1%	3%	31%	7%
	OD: lymphoma	1%	2%	2% (Null cells)	<1%	1%	1%	<1%
3	Lymphoma	41%	3%	36% (Mixed T-cell)	–	4%	–	0
4	Lymphoma	0	0	0 (Null cells)	11%	4%	–	0
5	Lymphoma	3%	3%	5% (Null cells)	–	7%	–	0
6	Lymphoma	10	15	52% (Polyclonal)	–	48%	–	0
		T-rosette	Surface IgG	Lambda	Kappa			
7	Lymphoma	90%	0	0 (T-cells)	0			
8	Lymphoma	0	0	0 (Null cells)	0			
9	Lymphoma	0	0	0 (Null cells)	0			

Leu2=T cell (cytotoxic/suppressor subset). Leu3=T cell (helper/inducer subset). Leu4=total T cells. Leu11=natural killer cells. Leu16=B cells. Dr and IL2=activated cells; partially B-cells. Rosette=sheep rosette for T-cells. Ig, lambda, kappa=B cell markers.

limits the use of lymphocyte marker analysis as a method of diagnosing intraocular lymphoma The reasons for the apparent lack of tumour cell monoclonality are not clear. It is possible that a normal population of inflammatory cells is admixed with the tumour population to produce much of the heterogeneity observed[21,22] In previous studies of intraocular lymphomas an admixture of benign inflammatory cells has been noted.[5,23-25] A second explanation could be the presence of a biclonal or triclonal population of malignant cells.[26] Recent data from other laboratories have demonstrated the efficacy of Southern blot analysis in the detection of lymphoma cells. That technique, which was not used in this study, is a more sensitive means of detecting tumour monoclonality even when there is an admixture of normal cells.[22,26,27]

The origin and derivation of the cells which produce intraocular lymphoma are not clear.[9,14] It is apparent from our studies that these cells are derived from different lymphocyte populations, often admixed with normal inflammatory cells. Some cells are not classifiable with the surface antigens we have used in this study. Probably these null cells represent neoplastic transformation of either lymphocytes or other pluripotential cells which have transformed at an early stage of differentiation. In this study, with the exception of a marginal correlation ($p<0\cdot05$) between the number of B-cells expressing the Leu 16 marker and abnormal cells counted cytologically, no other correlations between immunological parameters and other cytological factors were observed.

The second major finding in this study was that a single vitreous biopsy was not always diagnostic. We have examined specimens from other institutions in which an inadvertent false negative cytological diagnosis occurred. Similarly, we have examined specimens from eyes in which we could not establish the diagnosis on the basis of cytological evaluation of a vitreous biopsy, yet the patient eventually was shown to have ocular lymphoma.[28] In our series two patients required bilateral vitrectomies before the diagnosis could be established. Vitreous biopsy and analysis of the vitrectomy fluid from the clinically more involved eye was not diagnostic.

The third finding that is clinically important is the observation that processing vitrectomy material directly from a needle aspirate resulted in better morphological detail then vitreous cells obtained from the suction reservoir of the vitrectomy instrument. It is uncertain whether the degradation of cellular detail was from the irrigation solution or the mechanical action of the vitreous cutter, but optimisation of cell preservation is important to establish the correct diagnosis

Most reports have stressed the almost uniform fatality associated with ocular lymphoma. We have previously reported on successful cure of this condition when diagnosed and treated with aggressive radiation and chemotherapy[1] It is apparent that even with modern diagnostic methods it is difficult to diagnose this malignancy correctly. However, with the ability to treat and cure many of these patients, establishing an early diagnosis is of paramount importance.

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Primary myxoid liposarcoma of the orbit

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SUMMARY Orbital liposarcoma is a rare and usually unsuspected neoplasm. Over a five-year period three female patients aged 22, 71, and 77 years presented with primary myxoid liposarcoma of the orbit. The management of one patient was complicated by a history of orbital decompression for suspected thyroid eye disease. The tumour infiltrates locally beyond a deceptive pseudocapsule, and surgery has to be radical to be effective.

The orbit is a rare site for primary liposarcoma,[1] a tumour which usually originates in deep connective tissue planes and is most common in the thigh and retroperitoneum. Only 10 orbital cases have been reported in detail so far. Four were fatal and six survived to the date of reporting.

Three patients with differing clinical features of myxoid orbital liposarcoma presented to the Orbital Clinic at Moorfields Eye Hospital during the last five years. Their cases illustrate the difficulties which may be experienced in establishing both the diagnosis and the optimum treatment of this tumour. The rationale for surgical excision is discussed in relation to the histological type and the results of studies of systemic liposarcoma.

Patients and methods

CASE 1

Two years prior to presentation at this clinic a 22-year-old woman developed a painful right proptosis of fairly rapid onset. Myxoedema was diagnosed at the time, and she was treated with thyroxine and systemic steroid for presumed thyroid eye disease. There was no further deterioration during treatment. Five months later the affected orbit was surgically decompressed into the ethmoid and maxillary sinuses, and after temporary improvement the right eye again became progressively proptosed.

When she was first seen in this clinic the visual acuities were 6/6 in both eyes. The right eye was 15 mm proptosed and displaced 10 mm downwards and 4 mm laterally. A firm mass could be palpated in the superomedial quadrant of the right orbit. The cranial nerves were intact apart from the finding of numbness in the medial part of the right upper eyelid. There was no lymphadenopathy.

High resolution computerised tomography confirmed orbital decompression and showed a large heterogeneous mass with areas of negative attenuation (Fig. 1) in the right orbit. A trans-septal orbital biopsy was performed under local anaesthesia.

Histological examination showed inflammatory tissue only. A second biopsy was taken through a

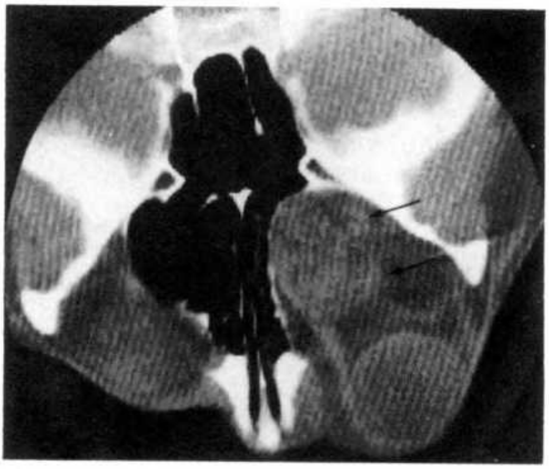

Fig. 1 *Axial CT scan in case 1 shows the following features: marked indentation of the ethmoid labyrinth on the affected side due to previous surgical decompression with prolapse of the tumour (arrows) into the decompression; areas of negative attenuation within the tumour mass indicative of the lipomatous nature of the tumour; a generalised increase in total orbital fat content on the affected side.*

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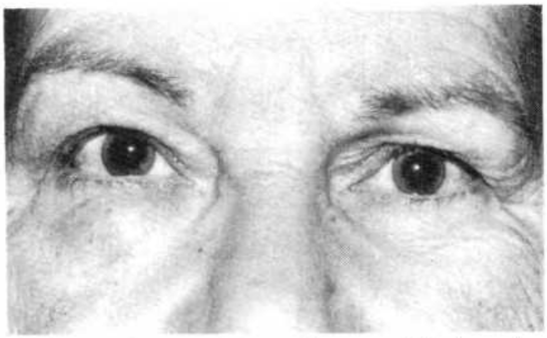

Fig. 2 *Case 2 at presentation, with a mass visible beneath the right lower lid.*

superomedial conjunctival incision under a general anaesthetic. The diffuse gelatinous tumour appeared to be adherent to and wrapped round the optic nerve and medial rectus muscle.

Initially the histological appearance of a loose, myxoid stroma infiltrated by some spindle shaped cells, eosinophils and mast cells, was suggestive of pseudotumour. However, the stroma contained some alcianophilic acid mucopolysaccharide, and electron microscopy showed many of the cells to contain lipid droplets. After the histological specimens had been referred to a number of centres a diagnosis of myxoid liposarcoma was made.

A short course of steroid therapy was initially given on the basis of the initial diagnosis. Following review of the histology radiotherapy in the form of 20·8 Gray of cobalt-60 treatment was administered. This was followed by craniofacial resection, which included the orbit and maxillary and ethmoidal sinuses. The patient remained alive and well two years later.

CASE 2

A 71-year-old woman noted increasing painless swelling of her right lower eyelid with occasional vertical diplopia over a period of 18 months. Her general health was excellent.

The visual acuities were 6/9 in both eyes with full fields to confrontation. A smooth, bluish swelling was seen below the right lower lid (Fig. 2), and a rubbery, non-tender mass measuring 15 by 30 mm could be palpated on the right orbital floor. There was 3 mm of right proptosis and 2 mm of upward displacement of the right globe, with dilated conjunctival vessels. The ocular movements were full, and there was no relative afferent pupillary defect. Both optic discs were normal. Radiographs showed no abnormality, but computerised tomography revealed an indistinct opaque mass on the floor of the right orbit. Anterior orbitotomy through the lower eyelid revealed an enormous gelatinous mass extending to the orbital apex and attached to the inferior oblique muscle and optic nerve. Subtotal excision was performed.

Histopathology showed a myxoid liposarcoma with delicate vascular channels, characteristic lipoblasts, very few mitoses, and some giant and pleomorphic cells (Fig. 3). Since the lesion was unlikely to be radiosensitive, further resection was considered necessary. However, on readmission for assessment three months later her symptoms had resolved. Retraction of the right upper eyelid had developed and was thought to be related to tethering of the inferior rectus. Computerised tomography showed no evidence of recurrence. Exenteration of the right orbit was suggested to the patient as the only means of ensuring complete removal of the tumour. This treatment was declined but the patient remained

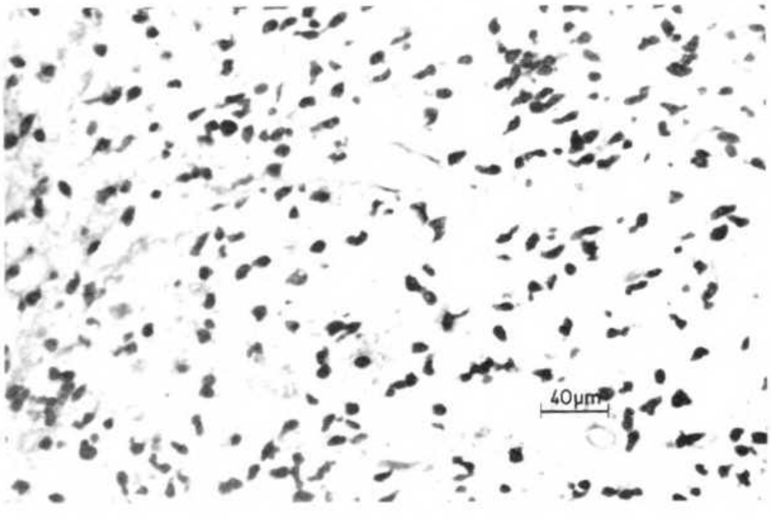

Fig. 3 *Histopathological section from case 2, showing a myxoid liposarcoma with delicate vascular channels, lipoblasts, a few mitotic figures and some giant or pleomorphic cells. H and E.*

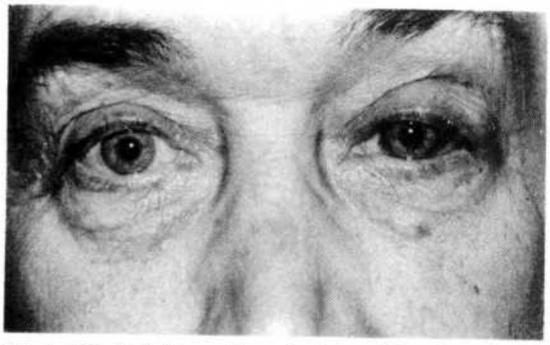

Fig. 4 *Clinical picture of case 3, with swelling above the left lateral canthus, 1 mm of ptosis, conjunctival melanosis, and frontalis overaction.*

asymptomatic when last seen in the clinic two years later.

CASE 3

A 77-year-old woman presented with lateral swelling of her right upper eyelid which had gradually increased over the previous nine months. Her general health was good.

On examination the visual acuities were 6/9 in the right and 6/4 in the left eye. A smooth, mobile, rubbery mass measuring 15 mm by 15 mm could be palpated in the superotemporal quadrant of the left orbit, but there was no displacement of the globe (Fig. 4). A millimetre of left blepharoptosis was associated with reduced function of the levator palpebrae superioris. Extensive conjunctival melanosis was present. Orbital *x*-rays were normal. An anterior trans-septal approach was used to biopsy a mass of gelatinous grey material involving the lacrimal gland.

Histological sections showed partial replacement of the lacrimal gland by stellate or spindle shaped cells and mast cells with a moderate degree of vascularity. There were multiple cytoplasmic vesicles characteristic of lipoblasts on electron microscopy (Fig. 5).

Computerised tomography failed to show residual tumour, but further gelatinous material was excised through an anterior approach. Complete removal would have required exenteration, but this was not considered justifiable because of the patient's age and slow tumour growth. Four months later she was stable with a left visual acuity of 6/9 and a comfortable eye with a poor tear film. However, two years after the initial presentation there was increasing

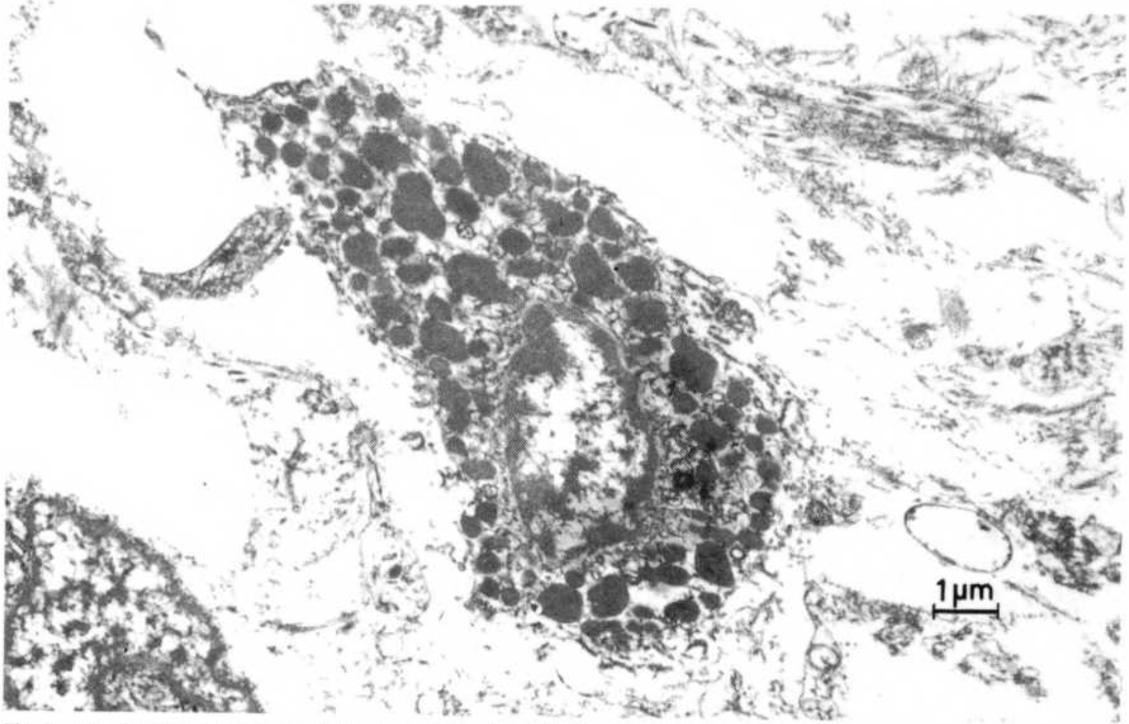

Fig. 5 *Case 3: electron micrograph showing a cell replete with intracytoplasmic lipid surrounded by a loose collagenous stroma.*

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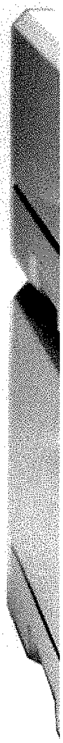

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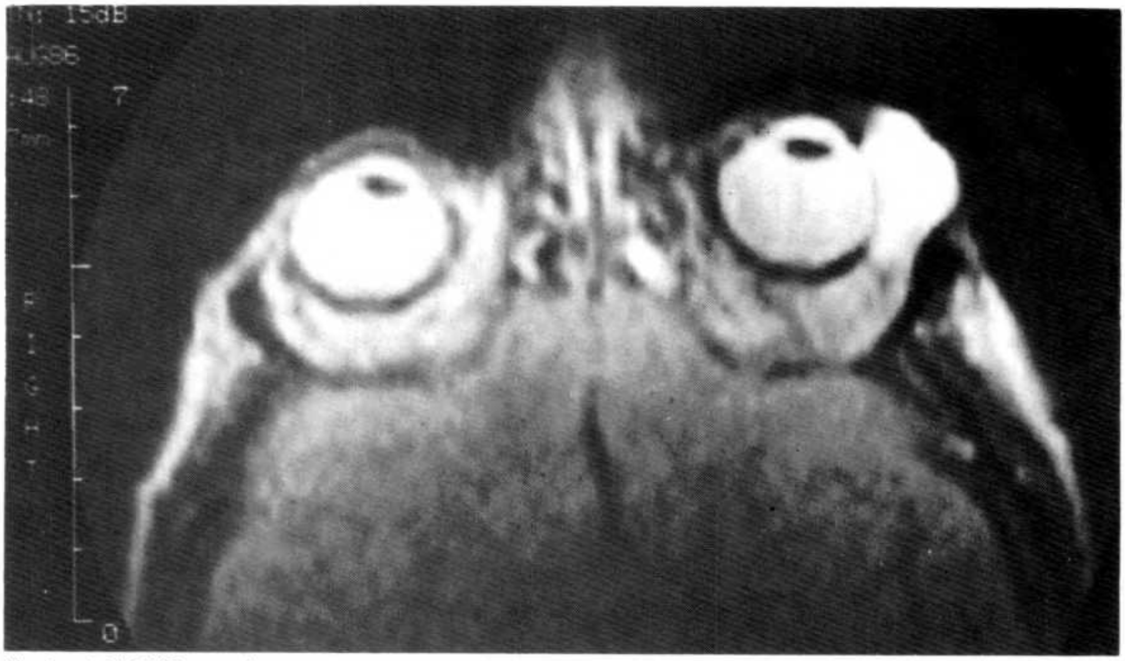

Fig. 6 *Axial NMR scan of recurrent tumour in case 3, showing a high signal intensity on T^2 weighted spin echo sequences. The centre of the tumour is shown much more intensely than surrounding orbital fat.*

discomfort with enlargement of the tumour. Nuclear magnetic resonance imaging revealed high signal intensity on T^2 weighted spin echo sequences (Fig. 6). The spin characteristics were not those of a fat containing tumour. The centre of the lesion was clearly distinguishable, but the margins were difficult to distinguish. To prevent further spread of the tumour total exenteration of the left orbit was performed. Tumour extended to the equator inferiorly and was demonstrated in the edge of the histological sections. When the patient was last seen two months after surgery the socket was healing without evidence of further infiltration.

Discussion

Orbital liposarcoma is rare and difficult to diagnose at presentation because of inconsistent clinical features. A review of the literature revealed only 10 convincing reports of the tumour. Strauss[2] described a case in the right orbit and Henderson[3] described two, but neither author specified the type. Quere *et al.*[4] and Citolli[5] cited fatal primary orbital liposarcoma in childhood and Mortada reported it in a 37-year-old man.[6] Only Citolli's case showed round cell preponderance. Stout's case[7] and another reported by Schroeder *et al.* in 1978[8] were myxoid. Jakobiec and Jones[9] reported two cases in which young women were treated with surgery and 50 Gray of radiotherapy; the first received both treatments but died six years later of generalised metastases, and the second was treated for recurrence; she remained well at the time of the report. An anaplastic orbital secondary from a well-differentiated abdominal liposarcoma has recently been reported.[10] The patient was treated by orbital exenteration but died shortly after surgery.

The first case described here presented with rapid onset of unilateral proptosis that was initially attributed to thyroid eye disease. Infiltration of the medial rectus muscle was interpreted as muscle enlargement at the time of orbital decompression, and the surgery facilitated tumour spread through the disrupted periosteum into the maxillary and ethmoid sinuses. At a later stage computerised tomography revealed a large heterogenous mass with areas of negative attenuation compatible with fat. The other two smaller tumours were not well delineated on CT scans. Magnetic resonance imaging was not consistent with a high fat content in the third case. This is consistent with the gelatinous consistency of the tumour and remarkable paucity of lipid vacuoles on histological sections. In all three cases the diagnosis was established only when biopsy of tissue was performed.

At surgery liposarcoma gives a false impression of being well circumscribed or even encapsulated, with a distinct lobulated pattern. The myxoid type appears gelatinous, and orange colouring has been reported, but the three presented here were grey. Less differentiated forms are brain-like with haemorrhages and cysts.

Histopathological diagnosis of liposarcoma frequently proves difficult, as the appearance may be confused with that of pseudotumour, lipoma, or myxoma. Lipoblasts, which support the diagnosis, are not always prominent. Since Virchow[11] first described myxoid liposarcoma 120 years ago, Stout[7] and Enterline *et al.*[12] have further classified the tumour, regarding it as one of the less malignant forms of liposarcoma.

The most recent Armed Forces Institute of Pathology (AFIP) classification by Enzinger and Weiss[13] is based on the stage of lipoblast development, manifest by the proportions of cellular lipid and mucinous material in the extracellular spaces and the overall degree of cellularity and cellular pleomorphism. Enzinger and Weiss believe that the neoplasm takes its origin from primitive mesenchymal cells rather than mature adipose tissue. Myxoid liposarcoma, accounting for 40 to 50% of cases, comprises lipoblasts, including a characteristic 'signet ring' type, at all stages particularly at the tumour margin and a mucopolysaccharide matrix with a delicate capillary network. The paucity of mitotic figures may contrast with rapid growth. Round cell liposarcoma has fewer apparent blood vessels and myxoid tissue with aggressive cellular proliferation and a tendency to metastasise. Well-differentiated liposarcoma usually resembles lipoma, though inflammatory cell infiltrates and fibrosis may occur. The dedifferentiated type occurs in only 5% of cases and metastasises in half of those, frequently producing both poorly and well differentiated deposits. Pleomorphic liposarcoma may feature eosinophilic giant cells similar to those in pleomorphic rhabdomyosarcoma or, less frequently, haphazardly arranged cells containing varying amounts of lipid.

In his series of liposarcoma of the lower limb and retroperitoneum Enterline *et al*[12] found the peak incidence to be between 40 and 60 years of age with a slight preponderance of males and higher proportion of myxoid tumours in young people. Enzinger and Winslow[14] noted an increased proportion of well-differentiated and pleomorphic forms in older people. The 13 primary orbital liposarcomas described to date comprise seven males and six females ranging in age from 5 to 77 years, mean 35 years. Myxoid tumours were found in six, but the tumour type was not related to age Local wide excision of liposarcoma occurring elsewhere in the body is advocated by most authors.[12 15–17] Enterline *et al*[12] reported that myxoid tumours seemed to be the most radiosensitive whereas Spittle *et al.*[16] was impressed by the response of poorly differentiated forms.

Kindblom *et al.*[18] in a recent large series of systemic liposarcomas assessed the results of treatment in 77 patients; all had been treated by surgical excision of liposarcoma, and 27 had also received radiotherapy A marked difference was found between the prognosis for well-differentiated and myxoid types (12/17 and 12/20 10-year survival respectively) and that for round cell and pleomorphic liposarcomas (1/13 and 0/21 10-year survival respectively). Tumour site, size, and completeness of excision had the greatest effect on prognosis, but radiotherapy did not significantly affect it.

Trials of chemotherapy have been discouraging. Spittle *et al.*[16] reported one anecdotal case of pleomorphic liposarcoma with pulmonary metastases which responded to chemotherapy. Gottlieb *et al.*[19] achieved complete remission in three out of seven cases of liposarcoma treated with both adriamycin and dimethyl triazenoimidazole carboxamide. Cytotoxic treatment is unlikely to influence myxoid liposarcoma because it has a slow rate of spread.

CONCLUSIONS

Orbital liposarcoma is a rare tumour which presents difficulties with clinical and histopathological diagnosis. The paucity of data on treatment for a neoplasm that is surprisingly aggressive leaves the clinician with a therapeutic dilemma. The management decision should be clarified by careful determination of the histological subtype, which is of the utmost importance in predicting the prognosis.

The aggressive pleomorphic and round cell types require radical surgery in all cases. In our opinion the commoner myxoid types necessitate exenteration or midfacial resection as a life-saving procedure in a young person. In elderly patients there may be a satisfactory, though probably temporary, response to local resection. Radical surgery should be performed if there is continued growth with increasing discomfort. Radiotherapy is considered to be relatively ineffective in the treatment of this tumour. ■

We are grateful to Dr G A S Lloyd for providing and interpreting the CT scan in case 1 and to the Department of Medical Illustration for the clinical pictures.

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Bilaterality of tears of the retinal pigment epithelium

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SUMMARY Eyes with tears of detached retinal pigment epithelium have been studied for up to 10 years following the acute event. In a retrospective study it has been determined that such a lesion in one eye implies a high risk of a similar event occurring in the fellow eye. Patients with loss of vision in their second eye as a result of a pigment epithelial tear were also studied; in 10 of 22 patients a similar lesion could be identified in the first eye. These observations suggest that these patients have specific changes at the level of Bruch's membrane which predispose to this particular manifestation of age related macular disease.

Since they were first described in 1981[1] rips or tears of the retinal pigment epithelium have been recognised increasingly as a cause of severe central visual loss in age related macular degeneration.[2-14]

With continuing review of patients suffering an acute pigment epithelial tear in one eye we have observed or suspected this complication in fellow eyes frequently. Therefore we have sought to determine whether or not tears occur bilaterally more commonly than would be expected by chance alone.

Such a retrospective study requires that tears remain recognisable for some time after the acute event. In a previous study of 63 eyes it has been shown that these lesions undergo gradual modification over months to years.[15] The bed of the tear becomes replaced by a pale fibrous plaque or by pigment epithelium over a period of a few weeks. This is followed by progressive scarring and retinal pigment epithelial hyperplasia which gradually obscure the ophthalmoscopic features by which the original nature of the lesion can be recognised. More rapid modification of the appearance of the lesion occurs in the presence of choroidal neovascularisation, either preceding or following a rip, and of significant subretinal blood. From this review it was established that a lesion can be identified reliably as a tear of the pigment epithelium in 94% of cases after one year, 77% at two years, but in none after six years.

Patients and methods

A review of clinical and photographic records from the Retinal Diagnostic Department of Moorfields Eye Hospital between 1976 and 1986 was carried out to identify patients in whom the diagnosis of a pigment epithelial tear was made in at least one eye Diagnostic features of acute lesions were: (1) sharply defined pigment epithelial discontinuity; (2) an exposed area of Bruch's membrane and choroid denuded of overlying RPE (the 'bed' of the tear); (3) an elevated mound of pigment epithelial tissue adjacent to the bed; and (4) corresponding, sharply demarcated hypo- and hyperfluorescence on fluorescein angiography. More chronic lesions were recognised by characteristics established in the study of repair after acute tears.[15] Excluded from the study were patients aged less than 55 years as well as those with inadequate photographic or clinical documentation.

Seventy-three individuals were diagnosed as having a pigment epithelial tear in at least one eye; 41 were females aged 56 to 84 years (mean 70·6 years), and 32 males aged 55 to 82 years (mean 71 years). Photographic, angiographic, and clinical data were evaluated on all 73 patients. Eleven were excluded because of opaque media in one eye, the application of laser photocoagulation to a pigment epithelial detachment, or inadequate documentation. The length of review ranged from one to 126 months. In 1986 all subjects were invited for further examination in order to provide as long a period of review as possible.

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Results

Forty-five of the 62 patients had bilateral visual loss either at presentation or lost vision in the second eye during the review period (Table 1).

Of the 40 patients who were seen initially with a pigment epithelial tear in one eye and contralateral good vision 23 lost vision in the second eye during the period of review, 14 from a tear of the pigment epithelium, four from primary neovascular disciform lesions, two from undetermined cause, one from geographic atrophy, and two from long-standing pigment epithelial detachment. The remainder retained useful vision in the contralateral eye. All had drusen, and some had atrophy or detachment of the pigment epithelium at the most recent review.

Table 1 *Cause of visual loss in the contralateral eye in those patients with bilateral visual loss*

Visual loss at presentation	*Total*	*Tear*	*NV*	*Other*	*Uncertain*
First eye	23	14	4	3	2
Second eye	22	10	4	0	8

NV subretinal neovascular lesion

At presentation 22 patients had prior loss of central vision in the first eye at the time of diagnosis of a tear in the second. The nature of the lesion in the first eye was sought. A pigment epithelial tear could be diagnosed with assurance on the basis of clinical appearance and angiography in 10. Choroidal neovascularisation was evident as the primary event in four eyes. In the remaining eight, many of whom were seen three years or more after loss of vision, it was not possible to distinguish between a pigment epithelial tear and a primary neovascular disciform lesion in the eye with prior visual loss.

Discussion

This study implies that pigment epithelial tears occur frequently in both eyes; of the 45 patients with bilateral visual loss 24 had evidence of a tear in each eye True bilaterality may be somewhat higher, since in eight patients one eye was examined late in the evolution of the lesion, at a time when a tear would no longer be identifiable. This can be compared with an estimated 1% risk of loss of vision in both eyes due to a tear if bilateral involvement were due to chance alone In a hospital based population survey it was found that pigment epithelial detachments comprised approximately 10% of exudative macular lesions in age related macular disease,[16] and in a natural history study 10% pigment epithelial detachments sustained a tear.[9]

The high prevalence of bilaterality of pigment epithelial rips suggests that these patients may have particular attributes of age related change at the level of Bruch's membrane which lead to this complication. That the specific changes required to produce this complication might affect both eyes similarly would be expected given the demonstrated symmetry of drusen as a clinical manifestation of age related macular disease [17,18]

The hypothesis that these patients have Bruch's membrane changes which differ from those which precipitate other complications of age related disease[9] now appears to be testable This could be achieved by documenting the fundus changes in the fellow eyes of those with a retinal pigment epithelial tear, since this study shows that these eyes have a high risk of suffering a similar fate.

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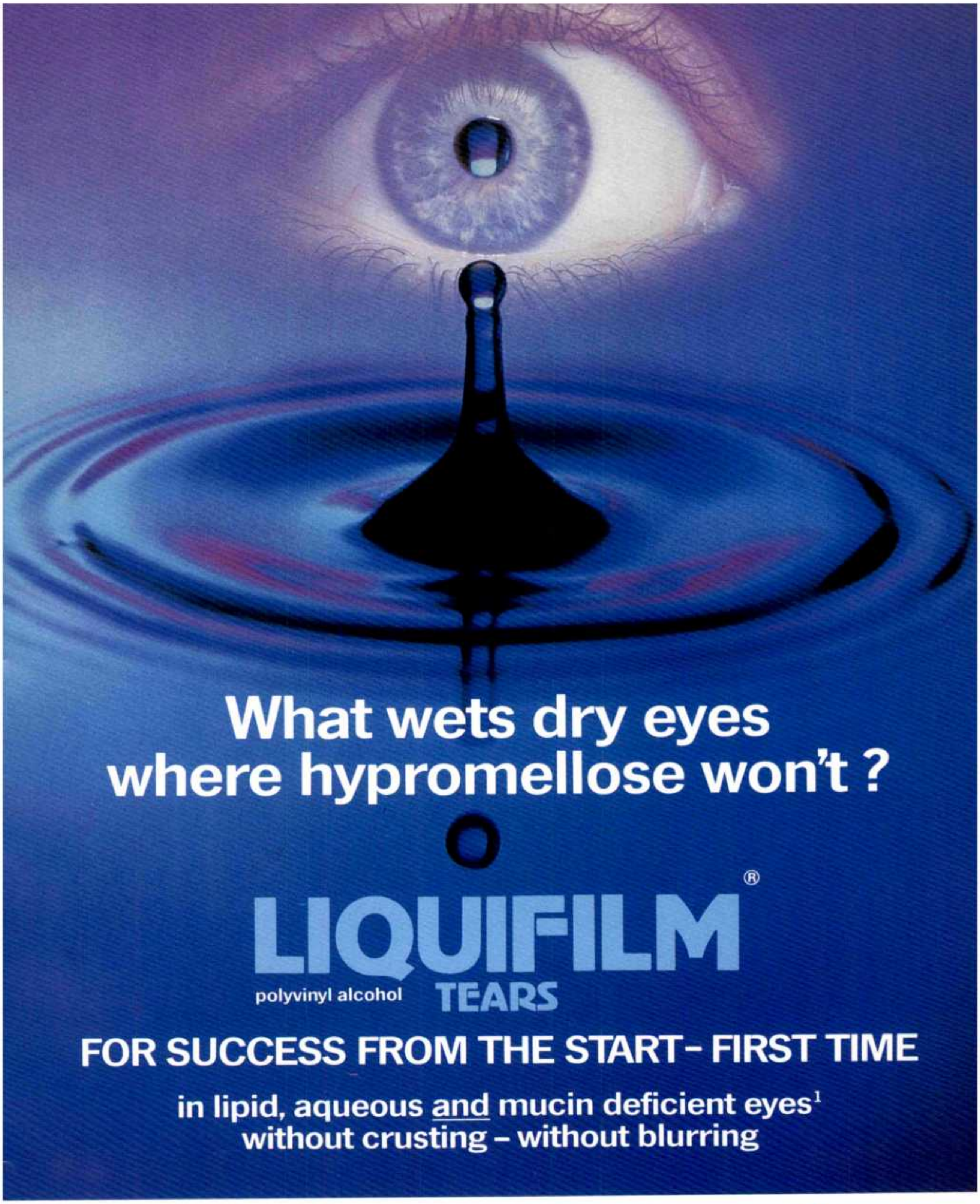
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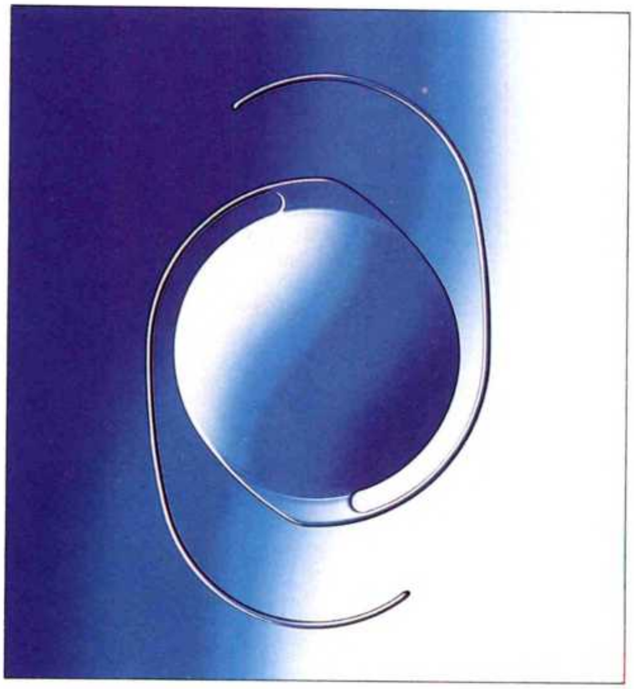

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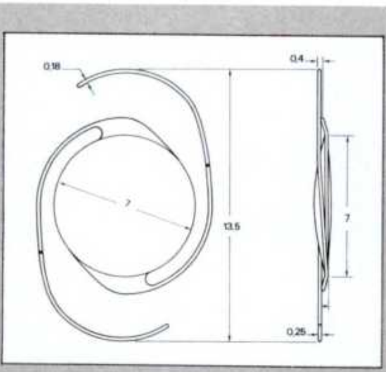

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High incidence of corneal epithelium antibodies in Fuchs' heterochromic cyclitis

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R VAN DER GAAG, AND A KIJLSTRA

From the Netherlands Ophthalmic Research Institute, Amsterdam

SUMMARY Sera obtained from 26 patients with Fuchs' heterochromic cyclitis were examined for the presence of autoantibodies directed against the anterior segment of the eye by means of immunofluorescence techniques. Antibodies against human iris tissue could not be detected, whereas autoantibodies against corneal epithelium were found in almost 90% of cases. This is the first report describing the presence of autoantibodies in patients with Fuchs' heterochromic cyclitis and it provides a further clue that immunological mechanisms might play an important role in the aetiology of Fuchs' heterochromic cyclitis.

Fuchs' heterochromic cyclitis is a relatively rare condition. According to Dernouchamps[1] it accounts for approximately 3% of all cases of uveitis. In 90% of the patients only one eye is affected.

The diagnosis is sometimes difficult, especially in the early stages of the disease. According to Fuchs[2] the essential features are a low grade cyclitis, including a variable degree of iris stroma atrophy, starting in the pupillary margin and causing depigmentation of the stroma. In later stages the iris pigment epithelium also becomes affected. Further clinical findings are the absence of synechiae and the presence of scattered, small, translucent keratic precipitates. Most of the patients visit the ophthalmologist with complaints of reduced vision which are caused by cataract formation or vitreous opacities.

The major causes of visual loss in heterochromic cyclitis are cataract and progressive glaucoma. Because glaucoma is a rare complication (15% of cases),[3] and cataract extraction results in the restoration of clear vision, the prognosis may be good.[4]

Various theories have been proposed to explain the aetiology of Fuchs' heterochromic cyclitis. Electron microscopic studies of iris biopsies from patients with the disease reveal a decreased number of melanocytes with relatively few, small melanin granules.[5] Earlier EM studies[6] and light microscopic studies[7] showed the presence of plasma cells and lymphocytes in the irides of these patients. The keratic precipitates, which are so typical of this disease, have been shown to represent an accumulation of lymphocytes.[8] Analysis of the aqueous humour from patients with this disease showed intraocular production of immunoglobulins; furthermore rheumatoid factor (RF) and immune-complex-like material could be detected.[9] These observations strongly suggest involvement of an immunological process in the pathogenesis of the disease.

To investigate the role of the immune system in this disease we examined the incidence of autoantibodies directed against the anterior segment of the eye. No antibodies could be detected against iris or ciliary body, but surprisingly a high percentage of patients (88%) had antibodies against corneal antigens.

Materials and methods

Sera were obtained from 26 patients with Fuchs' heterochromic cyclitis (13 males and 13 females, average age 37 years) visiting the eye clinics of the universities of Amsterdam and Rotterdam. The diagnosis was made when a patient presented with a low-grade uveitis characterised by the absence of synechiae, and more or less iris (stroma) atrophy with or without heterochromia, the typical keratic precipitates and often cataract. Thirty sera were also obtained from sex and age matched (healthy) persons without a history of ocular inflammation.

Sera were tested for the presence of iris, ciliary body, or cornea antibodies by an indirect immunofluorescence technique. Human irides, collected

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from donor eyes (from which the corneas were used for transplantation) and rabbit corneas were snap frozen in liquid nitrogen. Sections (8 μm) were cut in a cryostat, air dried on to glass slides previously coated with gelatin (1%) plus potassium-chromium (III) sulphate (0·1%) and fixed in acetone for 10 minutes. After being washed with phosphate buffered saline (PBS) the sections were incubated

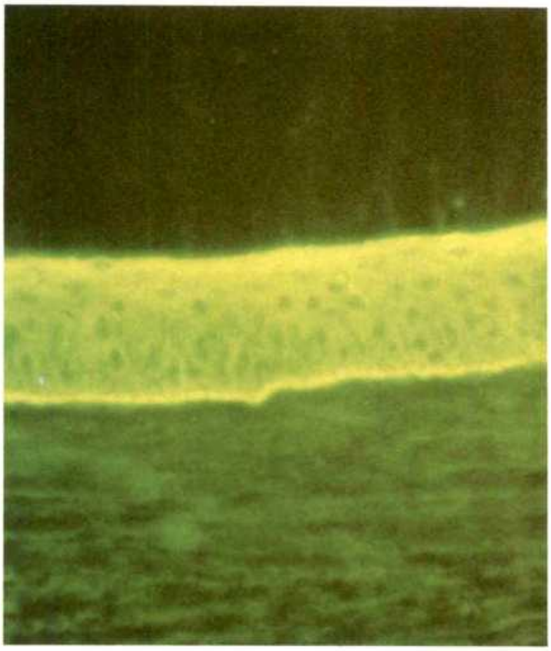

Fig. 1A

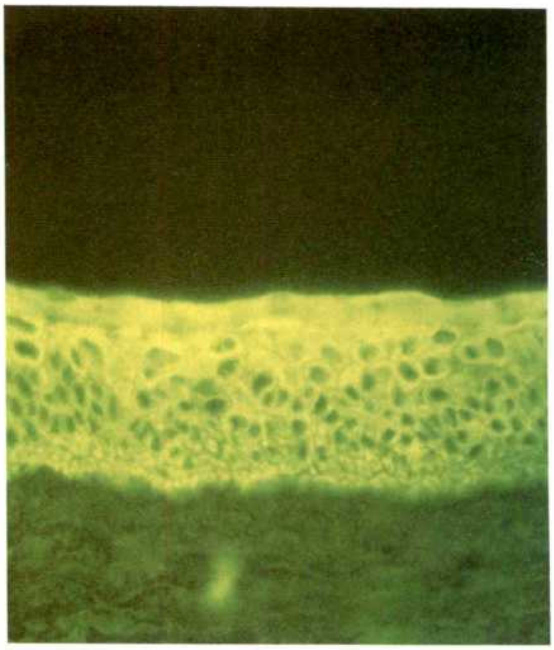

Fig. 1B

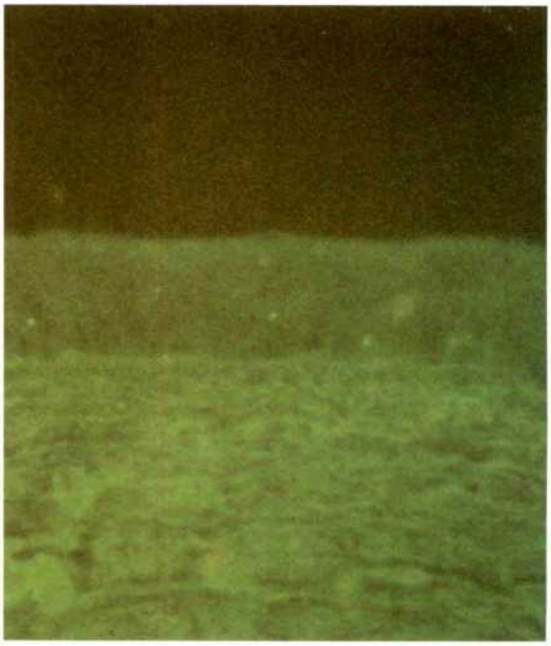

Fig. 1C

Fig. 1 A: *Immunofluorescence test showing antibodies in the serum of a patient with Fuchs' heterochromic cyclitis reacting with corneal epithelium.* B: *Positive serum of a healthy control.* C: *Negative serum of a healthy control.*

Table 1 *Antibodies to corneal epithelium in Fuchs' heterochromic cyclitis as tested by immunofluorescence*

	*Immunofluorescence score**			*Percentage positive*
	++	+	−	
Fuchs' patients (n=26)	18	5	3	88
Healthy controls (n=30)	1	0	29	3

*Tissue sections showing corneal epithelium antibodies after incubation with patient sera were scored by the following classification: strongly positive ++, positive +, negative −. The numbers indicate the number of patients.

with a 1/10 dilution of patient or control serum in PBS for 30 minutes at room temperature. Subsequently the slides were washed three times for 10 minutes with PBS and incubated for 30 minutes in the dark at room temperature with a polyclonal, FITC conjugated goat antihuman immunoglobulin (GAHuIg-FITC, Nordic, The Netherlands) or a monoclonal, FITC conjugated mouse antihuman IgG (MoAHuIgG-FITC, CLB, The Netherlands) (both diluted 1/40 in PBS). The slides were washed thoroughly and embedded in a solution of glycerin and PBS (1:1).

Human sera containing antinuclear antibodies were used as positive controls. Tissue sections incubated with PBS instead of human sera served as negative controls.

The slides were scored in a masked fashion by two different investigators, unaware whether patient or control sera were being used, with a Leitz fluorescence microscope using the following classification: strongly positive: ++, positive: +, negative: −.

Results

In the majority of patients with Fuchs' disease (88%; 23 out of 26) antibodies directed against corneal epithelium could be detected by the immunofluorescence test (IFT), whereas only one control person out of 30 had corneal antibodies (3%) (Table 1). The immunofluorescence pattern of this control person showed only cytoplasmic staining, while all the Fuchs' disease sera showed both cytoplasmic and membrane staining (Fig. 1).

Titration of the patients sera by a strong positive immunofluorescence test showed that corneal epithelium antibodies could still be detected up to a 1/40 serum dilution.

Some sera from patients with Fuchs' disease were also tested with a human cornea and a mouse cornea. These experiments showed similar results as those seen with rabbit corneas and are in agreement with earlier findings showing a large degree of cross reactivity between corneal antigens of different species.[10]

With the immunofluorescence test no antibodies could be detected in patients with Fuchs' disease (all 26 sera were tested) against normal human iris tissue. Positive control sera containing antinuclear antibodies showed a strong nuclear fluorescence staining in the iris. The detection of antibodies against human ciliary body was hindered by the fact that there was a strong background staining of endogenous immunoglobulins near the basement membrane and to a lesser degree also in the stroma (Fig. 2). This was apparent in control experiments whereby the tissue was incubated with phosphate buffered saline instead of human serum and subsequently

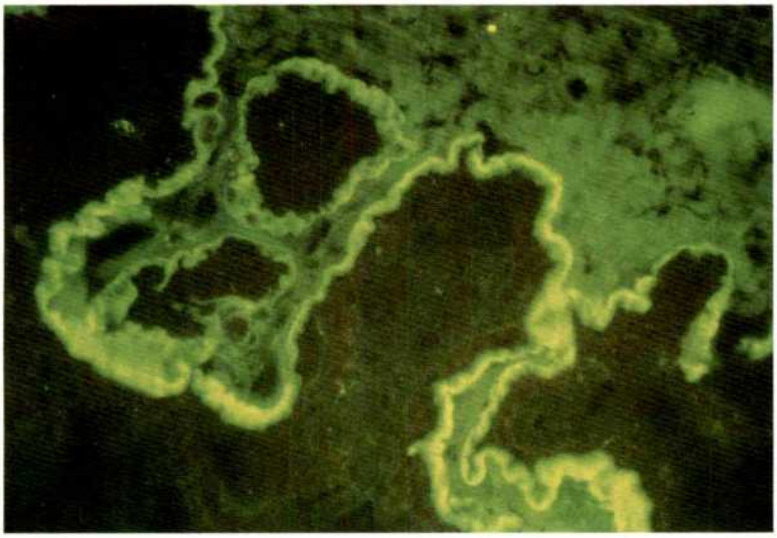

Fig. 2 *Incubation of normal human ciliary body with phosphate buffered saline followed by staining with fluorescein labelled goat antihuman immunoglobulins. Note strong staining of basement membrane.*

stained with fluorescein labelled goat antihuman immunoglobulins or a monoclonal antihuman immunoglobulin.

Discussion

Our results show a high incidence of corneal epithelium antibodies in the circulation of patients with Fuchs' heterochromic cyclitis.

Although the presence of circulating corneal epithelium antibodies has also been reported in other forms of uveitis, the incidence seen in patients with Fuchs' disease (88% positive) is much higher than that reported in other groups.[11,12] The incidence is 42% in anterior uveitis and 30% in posterior uveitis. The frequency of corneal epithelium antibodies in healthy controls was 3% in this study and is similar to that reported earlier.[11] Other recent investigations[13] into the presence of serum autoantibodies (which comprised smooth muscle, nuclear material, gastric parietal cell, reticulin, and mitochondria) in uveitis showed no difference between controls and patients with Fuchs' heterochromic cyclitis. Corneal epithelium antibodies are thus the first autoantibodies found in almost all patients with this disease, a finding which to our knowledge has not been reported earlier.

No antibodies could be detected against human iris The assay for antibodies against human ciliary body was not possible because this tissue already contains large deposits of immunoglobulins near the basement membrane and stromal regions. These findings are in agreement with recent investigations[14] showing that cationic immunoglobulins traverse the fenestrated capillaries in the ciliary body and bind to anionic sites within this tissue.

The detection of autoantibodies directed against a corneal layer not involved in Fuchs' cyclitis may appear puzzling at first sight. The corneal epithelium, however, contains a number of antigens which are shared with the corneal stroma and endothelium.[15–17] This layer is often involved in Fuchs' cyclitis, as shown by the small keratic precipitates which have been identified as accumulations of lymphocytes. These lymphocytes may be directed against certain antigens expressed or secreted by corneal endothelial cells. Furthermore it has been shown that the corneal epithelium shares antigens with the iris, ciliary body, and lens epithelium.[10,15–18] The fact that autoantibodies directed against the cornea mainly appear as corneal epithelium antibodies when using immunofluorescence techniques on cornea sections is probably due to the higher density of these antigens in the corneal epithelium as compared with stroma or endothelium.

It is not yet clear whether the corneal autoimmunity which was apparent in various forms of uveitis and especially in Fuchs' cyclitis is directed against the same antigen(s) or whether each entity has its own characteristic antigen. Furthermore it has not been clarified yet if the autoimmune reactions against corneal antigens have a primary role, implicating Fuchs' heterochromia as an autoimmune disease, or if these immunological reactions are a secondary phenomenon due to permeability changes in the anterior segment of the eye. The increased permeability of vessels in patients with Fuchs' disease can lead to a greater accessibility of corneal antigens to the immune system, which may result in an autoimmune response against these antigens. A possible important role of the immune system in Fuchs' heterochromic cyclitis is already apparent from the original description of plasma cells in the irides of these patients by Fuchs himself.[2] The accumulation of inflammatory cells on the endothelial side of the cornea is also in agreement with this hypothesis. Further evidence comes from studies by Dernouchamps,[19] who revealed the intraocular production of immunoglobulins in these patients. Whether the locally produced antibodies are directed against corneal antigens remains to be investigated. Rheumatoid factor and immune-complex-like material have also been observed in the aqueous humour of these patients.[9] The findings mentioned above in combination with our detection of corneal autoimmunity in such a high percentage of patients support the hypothesis that immunological mechanisms may play an important part in Fuchs' heterochromic cyclitis.

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Predisposing factors in microbial keratitis: the significance of contact lens wear

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SUMMARY Fifty-three patients consecutively admitted to Moorfields Eye Hospital for treatment of suspected microbial keratitis were examined to identify predisposing factors. The principal associations were pre-existing corneal disease (22 patients (41·5%)) and contact lens wear (22 patients (41·5%)). In 13 cases (25%) contact lens wear was the only factor in patients with otherwise healthy eyes using contact lenses as an alternative to spectacles. Gram-negative keratitis was more frequent in the lens wearers, with the exception of therapeutic lens users, than in other patients ($p=0{\cdot}0006$) and *Pseudomonas aeruginosa* caused keratitis in cosmetic soft lens users more frequently ($p=0{\cdot}001$). There was no correlation between lens handling or solution contamination in three extended wear soft-lens users. This implies that some soft-lens wearers may be infected by Gram-negative organisms from environmental sources other than contaminated lens care materials. Gram-negative keratitis is strongly associated with contact lens wear, and the diagnosis must be considered in any contact lens user with an acutely painful red eye.

Microbial keratitis remains a serious condition with significant morbidity. The predominant causative organisms in the UK are aerobic bacteria, but these and the predisposing factors vary throughout the world. Early diagnosis, identification of the responsible organism, and specific antimicrobial therapy are mandatory for effective treatment. This requires a high index of suspicion for a microbial cause of keratitis and knowledge of the likely causative organisms as well as reliable microbiological investigation and the administration of effective antibiotics in adequate dosages.[1]

Until the use of contact lenses became widespread as an alternative to spectacles microbial keratitis occurred in eyes with existing diseases of the ocular surface that predisposed to infection by disrupting ocular defence mechanisms,[2] corneal trauma and surgery, postherpetic corneal disease, bullous keratopathy, corneal anaesthesia, corneal exposure, and the dry eye being among the most important.[1-4] In the past contact lens wearers have made up only a small proportion of patients with this disease.[1-4] However since 1977[5] there have been reports of substantial numbers of cases of bacterial keratitis in wearers of soft contact lenses, mainly from the USA. The proportion of microbial ulcers attributed to lens wear has risen to over 30% in some centres in the 1980s,[6,7] making lens wear one of the major predisposing factors. This has not been the experience everywhere owing to differences in culture, referral pattern, case selection,[1,2,4] and lens wearing patterns. The disease in contact lens wearers is often caused by *Pseudomonas aeruginosa*, a virulent corneal pathogen,[7] resulting in severe morbidity. Most of these patients have normal eyes and are wearing lenses as an alternative to spectacles. Concern has been expressed by ophthalmologists[8] as well as by the lay press in the UK[9] and the USA[10] about this situation.

This prospective study was carried out to provide an up-to-date analysis of the most important predisposing factors and organisms in microbial keratitis at a major centre in the UK and to investigate epidemiological factors in the contact lens wearers.

Patients and methods

Fifty-three consecutive admissions to Moorfields Eye Hospital for microbial keratitis were assessed in a 10-month period between 25 February 1985 and 24 February 1986. Most cases of suspected microbial keratitis are admitted for treatment except those with

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minimal infiltrates not requiring intensive antibiotic therapy. These patients either were already being treated at Moorfields for other conditions when they developed microbial keratitis or presented from the area served by the hospital casualty department, with the exception of one secondary referral from another ophthalmic department. Scrapings from the affected area of cornea were taken routinely by the admitting surgeon for Gram-stain and culture on solid and in liquid media. Identification of the causative organism was confirmed by moderate growth of an organism in the streaks on one solid medium, growth of the same organism in more than one medium, or growth in one liquid medium that correlated with the Gram stain. Cases which did not meet these criteria, but in which a bacterial or fungal cause was treated presumptively were included, as failure to isolate an organism does not rule out a microbial cause.[2 11] Patients with a presumptive diagnosis of *Herpes simplex* virus keratitis were included only if a bacterial superinfection was suspected. The χ^2 test and two-tailed Fisher exact probability test were used to analyse proportional data where appropriate.

Results

CONDITIONS ASSOCIATED WITH MICROBIAL KERATITIS

These are shown in Table 1. Thirty-one cases were unrelated to contact lens wear, and, of these, 22 patients (41·5% of the total of 53) had pre-existing ocular surface disorders, 5 (9·4%) had had trauma or surgery, and 4 (7·5%) were a miscellaneous group with other associations. Of the patients in the group with ocular surface disorders, previous *Herpes simplex* virus keratitis resulting in secondary bacterial or fungal ulcerative keratitis, and bullous keratopathy accounted for over half. Several other conditions were represented among the remaining patients. In the traumatic and surgical group two patients developed keratitis following corneal abrasions, one following graft surgery, and two as a late complication of cataract surgery from abrasions due to loose nylon corneal sutures. There were four patients in the miscellaneous group, none of whom had normal eyes except for one patient with a myeloblastic disorder. Contact lenses were being worn immediately prior to the onset of keratitis in 22 patients (41·5%), who were using lenses for the following reasons: cosmetic (as an alternative to spectacles in low hypermetropia and myopia) 10 (18·9%), therapeutic (medically supervised treatment for ocular surface disorders) 6 (11·3%), aphakia 3 (5·7%), and keratoconus 3 (5·7%). Extended wear soft contact lenses (EWSCL) were used by 13 patients, daily wear soft contact lenses (DWSCL) by 5, and daily wear hard contact lenses (DWHCL) by 4.

Table 1 *Summary of patient associations*

Associations		*Nos*	*Subtotals*
Non-users of contact lens			31 (58·5%)
Pre-existing corneal disease			22 (41·5%)
	HSV keratitis	8	
	Bullous keratopathy	4	
	Cicatricial conjunctivitis	2	
	Dry eyes	2	
	Neurotrophic keratitis	2	
	Atopic eye disease	2	
	Leucoma	1	
	Exposure	1	
Trauma/postsurgical			5 (9·4%)
	Corneal abrasion	2	
	Lamellar graft	1	
	Loose cataract sutures	2	
Miscellaneous		4	4 (7·5%)
	Topical steroid use		
	Blind eye from glaucoma		
	Aphakia		
	Systemic disease		
Contact lens			22 (41·5%)
Cosmetic			10 (18·9%)
	DWSCL*	3 (5·7%)	
	EWSCL†	7 (13·2%)	
Aphakic	DWHCL‡/DWSCL/EWSCL	3	3 (5·7%)
Keratoconus			3 (5·7%)
	DWHCL	2	
	DWSCL	1	
Therapeutic			6 (11·3%)
	DWHCL	1	
	EWSCL	5 (9·4%)	
Total			53

*Daily wear soft contact lens.

†Extended wear soft contact lens

‡Daily wear hard contact lens (polymethylmethacrylate and gas permeable)

No cases occurred in patients without potentially predisposing factors. The only patients with previously normal eyes were the cosmetic lens users and the patient with a myeloblastic disorder.

MORBIDITY

The age and sex of the study patients are given in Table 2. The cosmetic lens associated group are shown separately; they had otherwise normal eyes and would not have been under hospital supervision had they not developed keratitis. Their outpatient visits and time spent on treatment were directly attributable to the episode of keratitis (Table 2). Loss of vision in this group occurred in three patients with post resolution acuities of 6/12, 6/18, and perception of light, who claimed to have had normal vision before the episode. The patients in this study occupied a mean of 2·1 beds per day. This was 1·8% of the total number of available beds in the hospital, making this one of the principal causes of admission for medical treatment.

Table 2 *Morbidity*

		Cosmetic lens users (n=10)	*All patients (n=53)*
Age in years	Range	16–69	2 5–88
	Mean	35·4	52
Male female ratio		4 M 6 F	30 M:23 F
Days in hospital	Range	3–37	3–37
	Mean	9 5	12
Out patient visits	Range	2–>16	
	Mean	5	
Weeks on treatment	Range	2–>52	
	Mean	14	

MICROBIOLOGY

Corneal cultures were positive in 32 patients (60%). The frequency of positive cultures was the same in both contact lens and non-contact lens users (p>0·8). Corneal isolates from the study patients are shown in Table 3. Non-contact lens users were predominantly infected by Gram-positive cocci. The therapeutic contact lens (TCL) users were infected by the same spectrum of bacteria (p=0·391). However, the remaining contact lens users differed by being predominantly infected with Gram-negative bacteria when compared with the other patients (p=0·0006). *Pseudomonas* was the commonest Gram-negative bacterial isolate and occurred more frequently in these contact lens wearers (p=0·009), though it was most strongly associated with soft contact lens use (p=0·001). Two further cosmetic soft lens wearers, whose corneal cultures were negative, had *Pseudomonas* recovered from their conjunctiva and contact lens respectively but have not been included in this analysis because they did not meet the criteria for identification of the causative organism.

Table 3 *Corneal microbial isolates*

Bacteria	*Numbers*			
	Contact lens			*Others*
	*SCL**	*HCL†*	*TCL‡*	
Pure infections				
Gram-negative				
Pseudomonas sp				
P aeruginosa	4			
P fluorescens				1
Unidentified sp.				1
Moraxella lacunata		1		2
Unidentified Gram-neg bacilli	1			1
Serratia marcescens		1		
Klebsiella oxytoca			1	
Proteus mirabilis				1
Gram-positive				
Staphylococcus pyogenes				2
Staphylococcus epidermidis			1	
alpha-haemolytic streptococci			1	
beta-haemolytic streptococci				3
Streptococcus pneumoniae			1	2
Diptheroids			1	1
Mixed bacterial infections				
Gram-negative				
P aeruginosa+Gram-neg rod	1			
Gram-positive and negative				
Moraxella+Micrococcus				1
Gram-positive				
S pyogenes+S viridans				1
S epidermidis+alpha-streptococcus+diptheroid				1
Fungal infections				
Candida albicans				1
Aspergillus fumigatus				1
Subtotals	6	2	5	19
Total				32

*Soft contact lenses (all cosmetic daily and extended wear)
†Hard contact lenses (aphakia and keratoconus daily wear)
‡Therapeutic contact lenses (hard daily and soft extended wear).

CONTACT LENS HYGIENE AND ITS CORRELATION WITH OCULAR BACTERIAL ISOLATES

Fourteen contact lens users had their hygiene regimen evaluated by interview and their lens cases and solutions cultured when these could be obtained. The same organism was grown from two DWSCL patients' cases as from their cornea. Three EWSCL patients had not handled their lenses for four to 42 days before the onset of their symptoms. In one of these cases *Ps. aeruginosa* was isolated from the corneal cultures and in another from the conjunctival cultures only. The third patient had keratitis, typical of Gram-negative infection, from which no organism could be recovered. All the lens solutions and eye drops used by these patients were sterile. The lens case was cultured from the patient with a conjunctival isolate of *Pseudomonas* but was contaminated with different Gram-negative bacteria.

Discussion

There have been few studies on the frequency of factors predisposing to corneal ulcers. This study has confirmed that bacterial keratitis is rare in patients with normal eyes[1-4] except in cosmetic contact lens users, and has shown that the use of contact lenses is now a major predisposing factor in microbial keratitis at one centre in the UK. The proportion of lens wearers affected is the largest reported so far, though there are comparable figures from previous reports in the USA.[6,7] 25% of the patients in this study were using contact lenses for cosmetic reasons or for aphakia when spectacles or, in unilateral aphakes, an intraocular lens implant would have been an appropriate form of correction. Their episode of keratitis resulted in considerable morbidity. The principal predisposing factors in patients who did not use contact lenses were the same in this study as in those published from similar centres in the last 15 years.[1-4]

This study differed from some earlier reports[1,4] in that only one patient was a secondary referral for the management of microbial keratitis. All remaining patients were either already being treated at the hospital for predisposing disorders, or were admitted as self referrals or as referrals from general practitioners. These patients are probably typical of those with severe microbial keratitis in any metropolitan region in the UK.

The recovery rate of 60% for bacteria from corneal cultures is similar to that in other studies,[4,7,11] as is the similarity in the spectrum of bacteria causing keratitis in therapeutic lens users and non-wearers of lenses.[7,12] The high proportion of soft-contact lens wearers infected by Pseudomonas has been noted in all studies reporting substantial numbers of contact lens wearers,[4-7,11,12] though *Staphylococcus* and Gram-negative organisms other than *Pseudomonas* are also important.[5,7,12] In this study statistical analysis shows that the frequency of *Pseudomonas* keratitis in cosmetic and aphakic SCL users is high in comparison with all other patients ($p=0.001$); it did not occur in any of the four HCL users, in which group *Pseudomonas* has rarely been reported. Infection with other Gram-negative organisms occurred in the HCL users, and the proportion of infections due to all Gram-negative organisms was higher in all contact lens wearers, except therapeutic, than in the remaining patients ($p=0.0006$). These findings suggest that the use of any contact lens, except therapeutic, may have modified the spectrum of microbial keratitis found in the general population of people predisposed to the disease, and that soft lens users may be particularly predisposed to infection by *Pseudomonas*. This is of concern because *Pseudomonas* is the cause of the most severe fulminating keratitis and because most soft contact lenses are worn for 'cosmetic' purposes.

The risk of microbial keratitis associated with the different predisposing factors cannot be estimated from the type of study reported here because the size of the population at risk is unknown. However, the number of DWSCL and EWSCL users affected was higher than might be expected.[6-8,12] Although the proportion of microbial keratitis patients using contact lenses is now high at many centres, it must be emphasised that the risk of microbial keratitis to most contact lens users is low. Exceptions are the TCL group, who have ocular abnormalities which predispose them to ocular infection, and the aphakic EWSCL wearers in whom the risk of bacterial keratitis ranges from 1 to 6:100 patients per year.[13] There have been relatively few such studies on other lens types.[14-17] These are of doubtful value because of uncertainties about the criteria for microbial keratitis, the indications for lens wear, variations in wearing patterns, and the relatively few cases of keratitis reported. In the light of the epidemic of case reports of SCL keratitis it is possible that the upper estimates of microbial keratitis in SCL wear of around 1:1500 per patient year[16,17] and the lower estimates for HCL wear of between 1:6500 and 1:15 500 per eye per year[15] may be realistic. It is certain that well designed studies need to be done to confirm the magnitude of the relative risk and if possible the absolute risk for cosmetic lens users.

Differences in susceptibility to microbial keratitis for users of different lens types have not been explained. *Pseudomonas*, like most bacteria, requires an epithelial defect for corneal invasion.[18] Such defects occur in all lens wearers at times.[15] Bacterial contamination of lens care solutions and cases has been shown to occur in normal SCL users[19] and arises from organisms, including *Pseudomonas*, that are ubiquitous in our environment.[20] It is known that this may result in a large ocular inoculum. Many reports have shown a relationship between the corneal isolate and lens care material contamination,[5,21-23] as in the two DWSCL users in this study. Bacteriological typing has confirmed this relationship beyond doubt,[24] suggesting that improved lens hygiene will decrease the risk of keratitis.[19-21] However, little emphasis has been given to cases in which no relationship can be shown between the corneal isolate, deficient hygiene, recent lens handling, and solution contamination, even though several studies have recorded such patients.[20-24] This occurred in three EWSCL users in this study and suggests that contamination of lens care materials may be irrelevant in some patients. This finding, together with the high frequency of *Pseudomonas* infection in SCL users, is evidence for the hypothesis that some patients wearing SCL may be uniquely susceptible to infection by 'background' levels of contamination from *Pseudomonas* or other Gram-negatives that do not affect normal people not wearing contact lenses. Recent studies of lens-bacteria interactions have shown that both Gram-positive and Gram-negative organisms may adhere to both hard and hydrogel lens surfaces[25] and possibly colonise the lens for prolonged periods.[26] It is probable that lens-eye-microbial interactions may be of greater importance than has been appreciated.[8,23] These may explain some of the findings not explained by the contamination of lens care materials alone.

Now that contact lens wear is the most common predisposing factor for microbial keratitis in patients with previously normal eyes, there is a need for more research into its epidemiology, pathogenesis, and prevention. Meanwhile it is important that Gram-negative keratitis is considered in the differential diagnosis of all patients using contact lenses who present with an acutely painful red eye. Early diagnosis and treatment are essential to reduce the morbidity in this potentially blinding disease.

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Solar retinopathy following religious rituals

MONIQUE HOPE-ROSS, STEPHEN TRAVERS, AND DAVID MOONEY

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SUMMARY Four cases of solar retinopathy due to sun gazing during religious rituals are reported. All four patients suffered irreversible visual loss.

In ancient times, Plato recorded Socrates's admonishment to avoid eclipse watching, yet it continues to be the major cause of solar retinopathy. We present a series of four patients who during religious rituals gazed at the sun for varying periods of time in an effort to witness an apparition. The purpose of this paper is to draw attention to the severity and permanent sequelae of solar retinopathy.

Case reports

CASE 1

A 58-year-old man presented to the Royal Victoria Eye and Ear Hospital in October 1985. He complained of blurred vision affecting both eyes and inability to read print directly in front of him. The onset of symptoms was a week prior to presentation. While praying at a statue of Our Lady in Monasterevin, Co. Kildare, he had gazed at the sun for approximately six minutes in an effort to see an apparition. It was a weak October sky and he was wearing untinted lenses. While he was staring at the sun it turned black, but he could still see the edges. He looked away, the black spots persisted, and his vision was blurred

On initial examination the corrected visual acuity was 6/18 in the right eye and 6/12 in the left eye. Slit-lamp examination gave normal results. Funduscopy revealed a yellow lesion at both foveas, surrounded by a circular red area (Figs. 1A, B).

When seen in February 1987, 16 months after the initial injury, he still complained of poor visual acuity, glare, and spots in front of both eyes. Corrected visual acuity was 6/12 in both eyes. Funduscopy revealed that the yellow lesion had disappeared and was replaced by a diffused pigmentary change in the perifoveal area. At the centre of each fovea there was a central 'hole-like' lesion (Figs. 2A, B).

CASE 2

A 39-year-old man presented to the RVEE Hospital, in October 1986. He complained of blurred vision and black spots in front of his left eye. He had recently returned from a pilgrimage to Medjugorje, Yugoslavia. On 30 September in the late afternoon he had stared at the sun and had seen a vision. The following day he stared at the sun hoping to see the vision again. In an effort to do so he stared at the sun for 45 minutes. While staring at the sun he noticed a black spot, and when he looked away the black spot persisted. His vision was extremely blurred and worsened over the next day He was unable to recognise people, but over the next week his vision improved.

On examination the best corrected visual acuity in the right eye was counting fingers and in the left eye was 6/9. The right eye had been divergent and amblyopic since childhood. The findings on slit-lamp examination were normal. Colour vision and Goldmann fields were normal. Funduscopy revealed a yellow lesion at the left fovea. This was surrounded by a red circular area. The right fundus was normal. Fluorescein angiography gave normal results.

On review in July 1987 he still complained of a black spot in front of his left eye. His visual acuity had returned to 6/5. Amsler grid testing confirmed the presence of a small central scotoma. Funduscopy revealed a pigmentary disturbance at the left fovea, with a honeycomb pattern.

CASE 3

A 23-year-old nurse presented to the RVEE Hospital in June 1987. She complained of blurred vision and persistent black spots in the central field of vision of both eyes.

The onset of her symptoms was five days prior to

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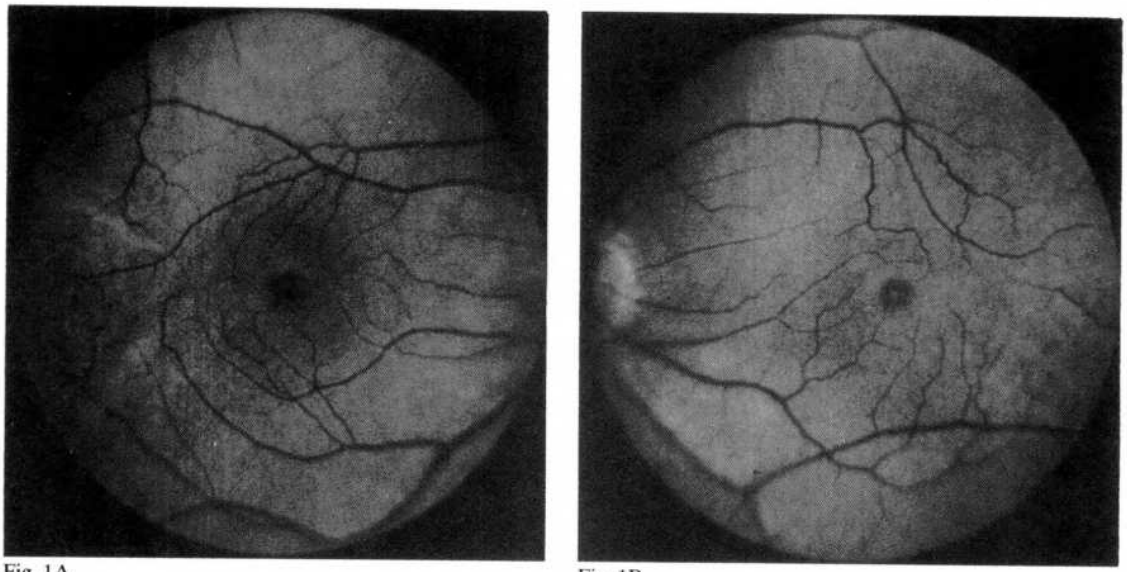

Fig. 1A

Fig. 1B

Fig. 1 (A, *right eye;* B, *left eye*): *Acute stage of solar retinopathy showing yellow lesion at both foveas, surrounded by a circular area.*

presentation. She had no previous ophthalmic history. While on a pilgrimage to Medjugorje she had stared at the sun for 10 minutes in the late afternoon of a hot summer's day. While staring at the sun it went a deep green, surrounded by a gold rim, and when she looked away her vision was blurred.

On initial examination the patient's visual acuity was 6/9 in both eyes. Amsler grid testing revealed bilateral central scotomata. Colour vision, pupils, and Goldmann fields were normal. Funduscopy revealed a yellow foveolar lesion and macular oedema in both eyes.

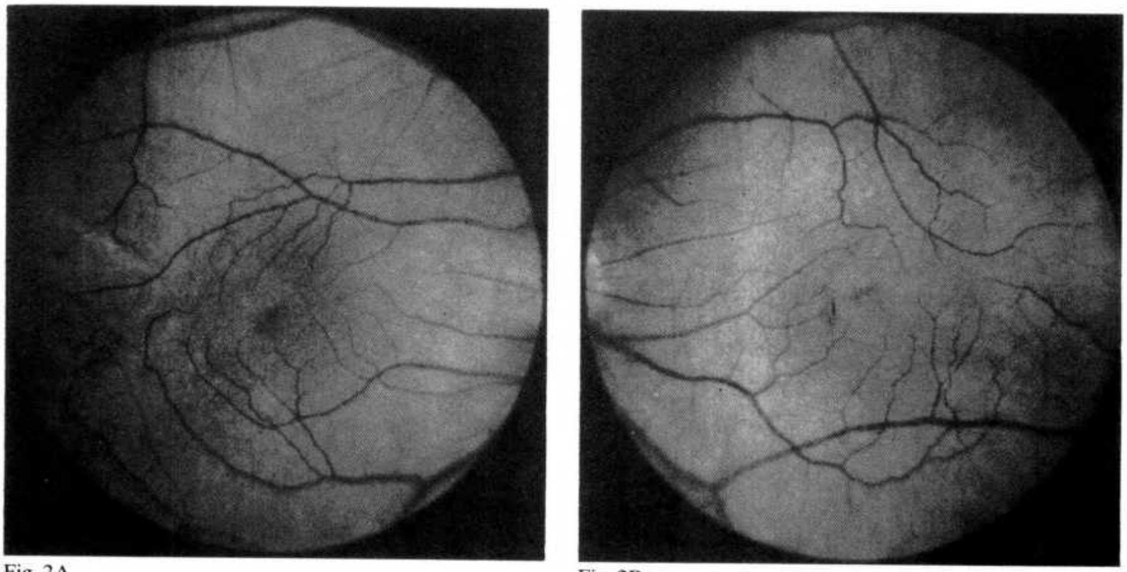

Fig. 2A

Fig. 2B

Fig. 2 (A, *right eye;* B, *left eye*): *Late stage of solar retinopathy showing diffuse pigmentary change in the perifoveal area, and a central 'hole-like' area.*

Three weeks after the initial injury the patient's visual acuity had returned to 6/6 in both eyes. She still complained of bilateral central scotomata, confirmed on Amsler grid testing. Funduscopy revealed slight pigmentary change at both foveas. Fluorescein angiography gave normal results.

CASE 4

A 33-year-old woman presented to the RVEE Hospital in July 1987. She complained of a black spot in front of her right eye. In May 1987 she had been on a pilgrimage to Medjugorje. She had stared at the sun at 7.00 pm intermittently for a few minutes. While she was so doing, the sun had danced and changed colour from orange to black to white. When she looked away she noticed her vision was blurred, and there was a black spot in front of her right eye. Gradually with time her vision improved, but the black spot has persisted.

On examination her visual acuity was 6/9 in the right eye and 6/12 in the left eye. The left eye had been convergent and amblyopic since childhood. The findings on slit-lamp examination were normal. Colour vision and Goldmann fields were normal. Amsler grid testing of the right eye showed a central and two small paracentral scotomata. The left fundus was normal. The right fundus showed an irregular pigmentary disturbance at the fovea and perifoveal area, surrounding a central 'hole-like' lesion.

Discussion

In the 1940s an entity termed foveomacular retinitis was found in large numbers of military recruits.[1] Abnormal findings were frequently bilateral and limited to the fovea and perifoveal area. In the acute stage there was loss of the foveal light reflex, macular oedema, and a yellow exudate. The foveal exudate resolved after 10–14 days. In the later stages a hole-like lesion at the fovea was surrounded by a perifoveal ring of coarse pigment.

The aetiology of this lesion was disputed and was attributed to localised disease of the choriocapillaris or vasomotor disturbances.[2,3] It is now generally accepted that the disorder was caused by sun gazing and is termed solar retinopathy.[4]

Eclipse watching is the commonest cause of solar retinopathy. It has also been described in sun bathers, pilots, military recruits, in cases of mental illness and drug abuse,[5-7] and following religious rituals. During religious rituals pilgrims may become oblivious to the ocular discomfort induced, and may stare at the sun for prolonged periods of time, incurring significant visual damage.

Solar retinopathy is usually bilateral. If there is pre-existing strabismus, damage is limited to the dominant eye. The prognosis for solar retinopathy is variable.[8] If there is early improvement in visual acuity, then full recovery may be expected within four to six weeks. Recovery to 6/6, however, may be accompanied by a permanent central or paracentral scotoma.

Solar retinopathy is due to a combination of thermal and photochemical injury. A relatively large proportion of the solar energy is concentrated in the blue end of the spectrum. It is thought that solar retinopathy is caused by the photochemical effects of the short wavelengths in the visible spectrum at 400–500 nm, with some thermal enhancement from the longer wavelengths in the infrared.[9] Experimentally it has been shown that the sensitivity of the retina to photic damage increases with a decrease in wavelength.[10] The basic photochemical mechanism underlying the sensitivity of the retina to short wavelengths of visible light is unknown. Several photochemical mechanisms may be responsible for the observed damage.

The brunt of injury is borne mainly by the outer retinal layers. In the early stages there is damage to the retinal pigment epithelium, with oedema, irregular pigmentation, and frank necrosis.[11] In the later stages there is focal loss of rod and cone nuclei and depigmentation of the retinal pigment epithelium.[12]

Spectral transmission of lenses reveals that a significant number of standard tinted lenses transmit unnecessarily high amounts of light in the ultraviolet, visible, and infrared portions of the spectrum.[13] These lenses offer no protection against retinal damage following direct observation of the sun. The only way to avoid solar retinopathy is to refrain from sun gazing. During an eclipse the public should be advised to view the sun indirectly using a pinhole camera.

We present here a series of four patients all of whom looked deliberately at the sun for prolonged periods of time. They were encouraged to do so by other pilgrims, who themselves had seen apparitions when staring at the sun. Two of the four patients were amblyopic in one eye, and suffered damage to the dominant eye. All four patients suffered irreversible visual damage, with persistent central scotomata.

We should ensure that the public is aware of the dangers of sun gazing—whether during religious rituals, sun bathing, or eclipse watching.

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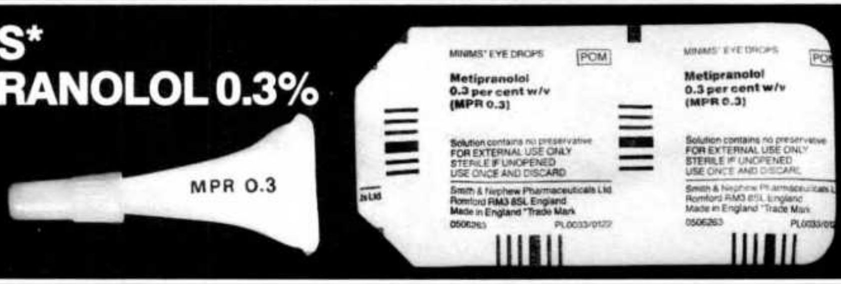

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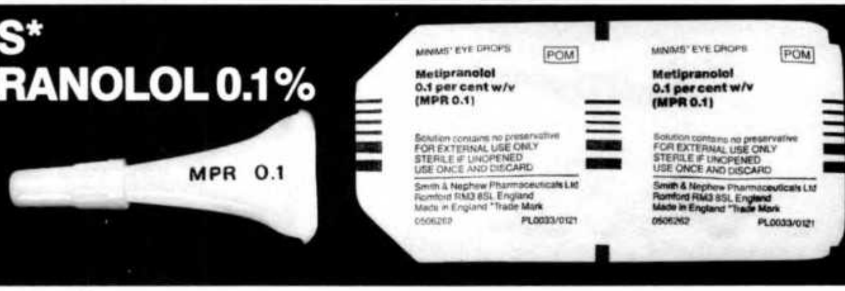

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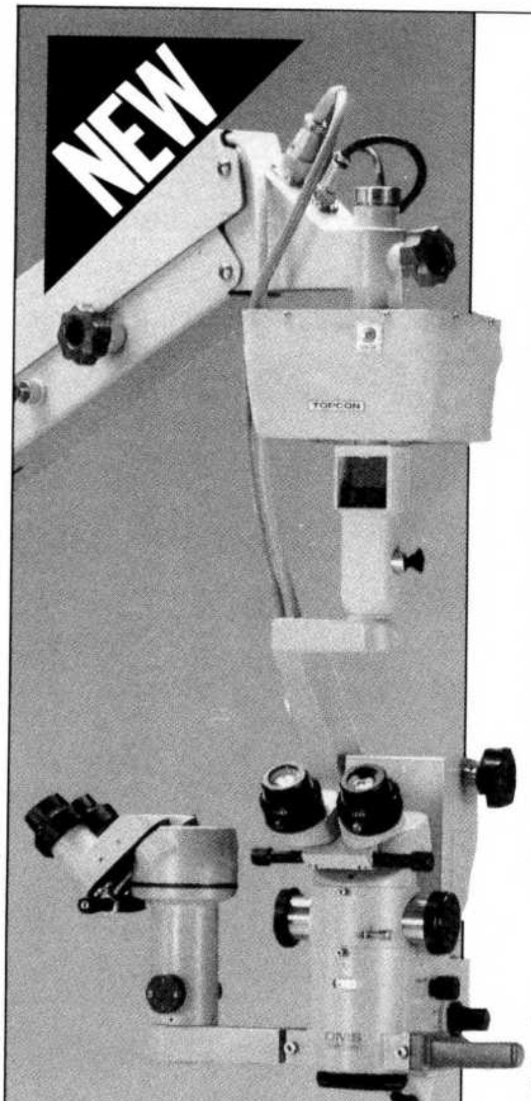

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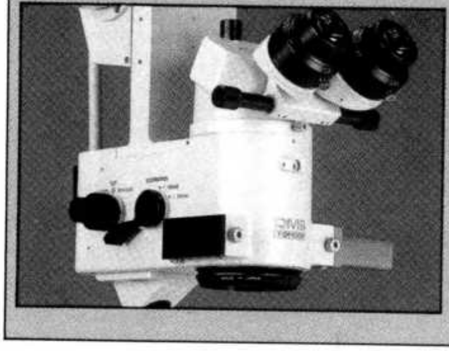

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Adrenaline dacryolith: detection by ultrasound examination of the nasolacrimal duct

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From the Departments of [1]Ophthalmology and [2]Pathology, University of Sheffield

SUMMARY A 73-year-old woman on topical pilocarpine and adrenaline for chronic simple glaucoma for three years presented with a mass in the medial canthus of the right eye. Although dacryocystography showed a dilated and partially obstructed nasolacrimal system, ultrasound examination was able to demonstrate a mass in the nasolacrimal duct. At operation a black dacryolith was found, of the diameter predicted by ultrasound. Histological examination of the dacryolith suggested its derivation from breakdown products of adrenaline.

Ultrasound examination of the nasolacrimal drainage system has been shown to be of value when the system is dilated in cases such as a mucocoele or acute dacryocystitis. It is of limited value in functional disorders, where the passage of fluid through the nasolacrimal system is slowed, producing a minimally dilated system.[1] No reports so far have illustrated the ability of ultrasound to demonstrate a mass in the nasolacrimal duct. This case illustrates the use of ultrasound in the detection of a solid mass in the nasolacrimal drainage system.

Case history

A 73-year-old retired nurse presented with chronic open-angle glaucoma in 1981, and she was treated with topical adrenaline 1% twice daily to both eyes. Four months later her intraocular pressures were found to be uncontrolled, and pilocarpine 4% four times daily was added to her medication to both eyes. In 1981 a left trabeculectomy was performed because of poor medical control. Pilocarpine and adrenaline were continued in the right eye. Because of travelling difficulties, from December 1981 her follow-up was continued at another unit. In 1986 she returned to this unit having suffered four episodes, over the previous eight months, of severe right-sided epiphora associated with a swelling over the right nasolacrimal duct She also noted the presence of a rusty discharge down the right nostril and reflux of this fluid into her right conjunctival sac. In between these acute episodes the epiphora and a slight swelling at the medial canthus persisted but were less troublesome. Her right nasolacrimal duct had been irrigated during one of these acute episodes, which had caused some resolution of her symptoms.

On examination a firm mass was palpable over the right lacrimal fossa extending slightly above the medial palpebral ligament. When the nasolacrimal system was cannulated through the lower punctum, the sac was entered easily. Irrigation with saline produced dilatation of the sac and a reflux of rust stained fluid through the upper punctum into the conjunctival sac. Cytological and microbiological examination of this fluid failed to show any abnormal cells or micro-organisms. The patient was unable to detect the passage of any fluid into the nasopharynx during irrigation.

A right dacryocystogram was performed (Fig. 1), which showed filling of superior and inferior canaliculi; contrast fluid drained into the lacrimal sac, where it collected in irregular, globular pools. No contrast fluid was seen to enter the nasopharynx. This suggested a chronic obstruction of the nasolacrimal duct causing dilatation of the nasolacrimal sac.

ULTRASONOGRAPHY

Ultrasonography of the right nasolacrimal duct was performed with a Sonumetric Ocuscan 400 hand-held ultrasound scanner with a 40° sector 10 MHz probe, set at 1550 m/s velocity and with an attenuation of 21 dB.

With the patient in a prone position the ultrasound probe was held against the lacrimal fossa at an angle

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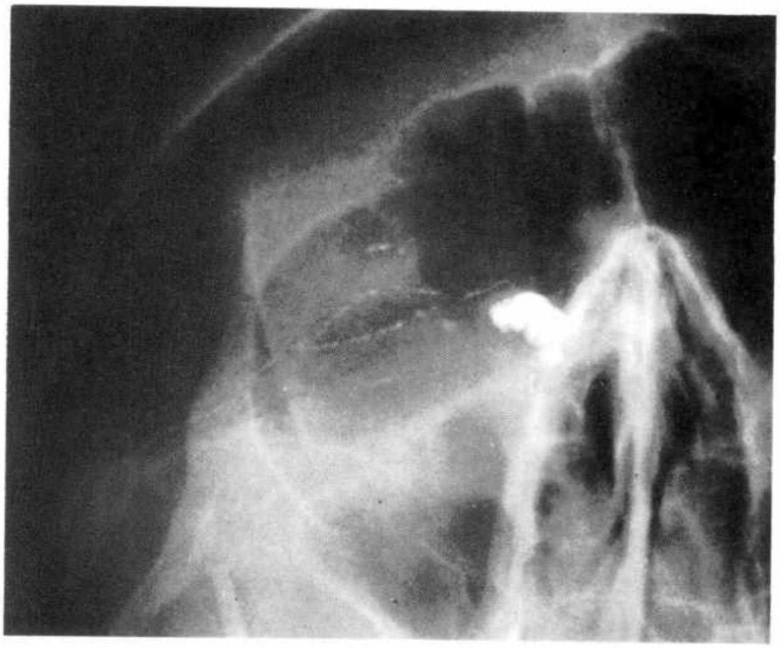

Fig. 1 *Right dacryocystogram. The contrast filled the superior and inferior canaliculi and drained into the lacrimal sac collecting in irregular globular pools. No contrast was seen to enter the nasopharynx.*

of 45° to the vertical to obtain both A and B scan images, which were photographed with a Polaroid camera.

The ultrasound examination showed a round mass in a dilated nasolacrimal sac (Fig. 2). The lesion had a poorly defined acoustic edge, with high internal reflectivity, and was not obviously attached to the wall of the sac, which had a normal appearance. The patient was admitted for exploration of the lacrimal sac under a general anaesthetic.

A slightly larger than standard dacryocystorhinostomy approach was employed to expose an enlarged, but otherwise normal looking lacrimal sac. A vertical incision was made into the sac; it revealed a solid black mass in its posterior-inferior portion, which extended down into the nasolacrimal duct. This lesion was removed in one piece with forceps (Fig. 3) to expose a grossly enlarged nasolacrimal duct. The posterior wall of the lacrimal sac looked slightly reddened and oedematous. A small biopsy was taken of this area and bacteriological swabs were taken for culture. A standard dacryocystorhinostomy was then performed.

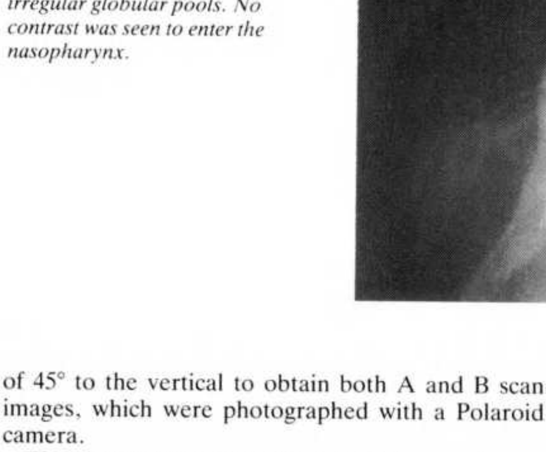

Fig. 2 *Ultrasound of right nasolacrimal sac: There is a mass in a dilated nasolacrimal sac. The mass has a poorly defined acoustic edge and high internal reflectivity. It is not attached to the wall of the sac.*

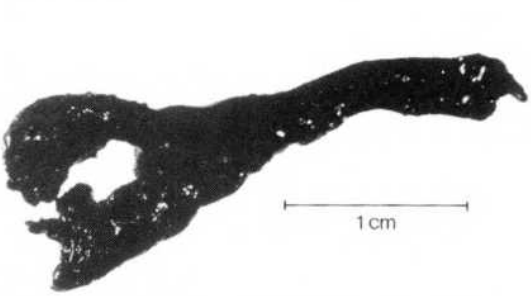

Fig. 3 *Adrenaline dacryolith. The dacryolith extended inferiorly into the nasolacrimal duct and superiorly into both superior and inferior canaliculi.*

HISTOLOGY

The dacryolith was black, 4·5 cm long and 0·75 cm in maximum diameter. Histologically it consisted of amorphous eosinophilic material, which was both argentaffin and argyrophilic positive and was thus consistent with a dacryolith containing a high proportion of degraded adrenaline. Histology of the sac biopsy revealed a chronically inflamed mucous epithelium with no evidence of infection or malignancy. Bacteriological culture of the swab taken from the lacrimal sac revealed a scanty growth of *Staphylococcus epidermidis*.

Discussion

Diagnostic ultrasound of the nasolacrimal system has been found to be useful in assessing the size of the sac and duct, the condition of their walls, and the type of fluid in the sac, for example, pus or mucus. It may prove to be of particular use in the diagnosis of solid lesions such as dacryoliths, tumours, and granulomas, which, though less common, can be difficult to diagnose preoperatively Ultrasound may prove a useful adjunct to dacryocystorhinostomy in such cases.

Dacryoliths are not uncommon if looked for carefully. Indeed Wilkins and Pressly[2] in their series of 94 dacryocystorhinostomies reported an overall incidence of 18%. In 25 cases of dacryoliths collected by Jones[3] epiphora was the commonest symptom followed by mucopurulent discharge. As in this case, irrigation of the lacrimal system may afford temporary relief, perhaps due to fragmentation of the dacryolith.

Both Jones[3] and Wilkins and Pressly[2] found the majority of patients to be below 50 years of age. In neither series were dacryoliths found to be caused by topical adrenaline therapy, which must remain an uncommon cause of nasolacrimal duct obstruction. Spaeth[4] describes three cases of dacryoliths, in patients with chronic simple glaucoma, who were treated with 2% adrenaline drops for at least one year. In all cases irrigation through the lower puncta caused the presentation of a dark plug into the nose or nasopharynx, which relieved the patient's symptoms. Analysis of the dark plug showed this to be derived from adrenaline.

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Yersinia-induced uveitis in Ireland

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SUMMARY A prospective study was undertaken on 54 patients with an apparently idiopathic first attack of acute anterior uveitis. Blood samples were assayed for antibodies to *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*, and tested for HLA type. Thirteen patients were found to have serological evidence of recent yersinia infection, eight with *Y. enterocolitica* and five with *Y. pseudotuberculosis*. The clinical course of uveitis did not differ from that typically found in HLA-B27 positive patients. Five patients were observed to develop non-ocular inflammation at a variable interval. The means by which eye inflammation follows yersinia infection is discussed in the light of recent theories on pathogenesis of HLA-B27 associated diseases.

Acute anterior uveitis (AAU) is defined as iridocyclitis lasting less than three months[1] and constitutes a significant proportion of all cases of uveitis. The incidence has recently been calculated at 8·2 new cases per 100 000 population.[2] The differential diagnosis of the precipitating cause has continued to change with new or more clearly defined clinical entities and improved laboratory diagnosis; however one recent retrospective analysis has shown that 43% of cases of AAU remain idiopathic.[3] Reported data on the prevalence of HLA-B27 in AAU vary, with an average of 50%, and the role of environmental and genetic factors in the pathogenesis of HLA-B27 associated disorders is not clear. It has long been suspected that AAU and related systemic inflammations result from a triggering agent acting across a mucosal surface such as the intestine. *Klebsiella* species have attracted particular interest, and variable recovery rates from faeces of AAU patients have suggested, but not confirmed, an association.[4,5] Two retrospective studies in Finland have reported AAU associated with yersinia infection.[6,7]

Yersiniae are Gram-negative rods. The genus comprises the species *Y. pestis*, *Y. enterocolitica*, and *Y. pseudotuberculosis*, and the latter two are divided into several serotypes. Yersiniae have the capacity to grow in refrigerator temperatures, and contaminated food is thought to be the most common route of infection.[8] *Y. enterocolitica* and *Y pseudotuberculosis* are intestinal pathogens causing acute enteritis but may initiate immunological complications such as erythema nodosum and arthritis. *Y. enterocolitica* and *Y. pseudotuberculosis* are endemic in Finland, where antibodies against them are found in 3 to 8% of the general population.[9] Yersiniae are not considered common pathogens in Britain or Ireland. However, a recent large survey in Dublin revealed that 31% of patients with acute appendicitis had serological evidence of yersinia infection.[10] Accordingly it was decided to undertake a prospective study of patients with AAU for evidence of yersinia infection.

Patients and methods

PATIENTS

Patients who presented between June 1985 and February 1987 with their first attack of AAU were eligible for inclusion in the study if no underlying cause was clinically evident. These patients had only eye symptoms. Patients were ineligible (1) if they had a prior diagnosis of a disease related to AAU, such as sarcoidosis or ankylosing spondylitis, or (2) if they had non-ocular symptoms, such as joint pain. Patients with chronic or primarily posterior uveitis were excluded. Fifty-four consecutive patients (35 male and 19 female) were recruited. The mean ages were 32·6 years for male patients and 30·2 for female patients.

Blood samples from the study group were compared with those from 120 healthy, asymptomatic controls. This control population was composed of

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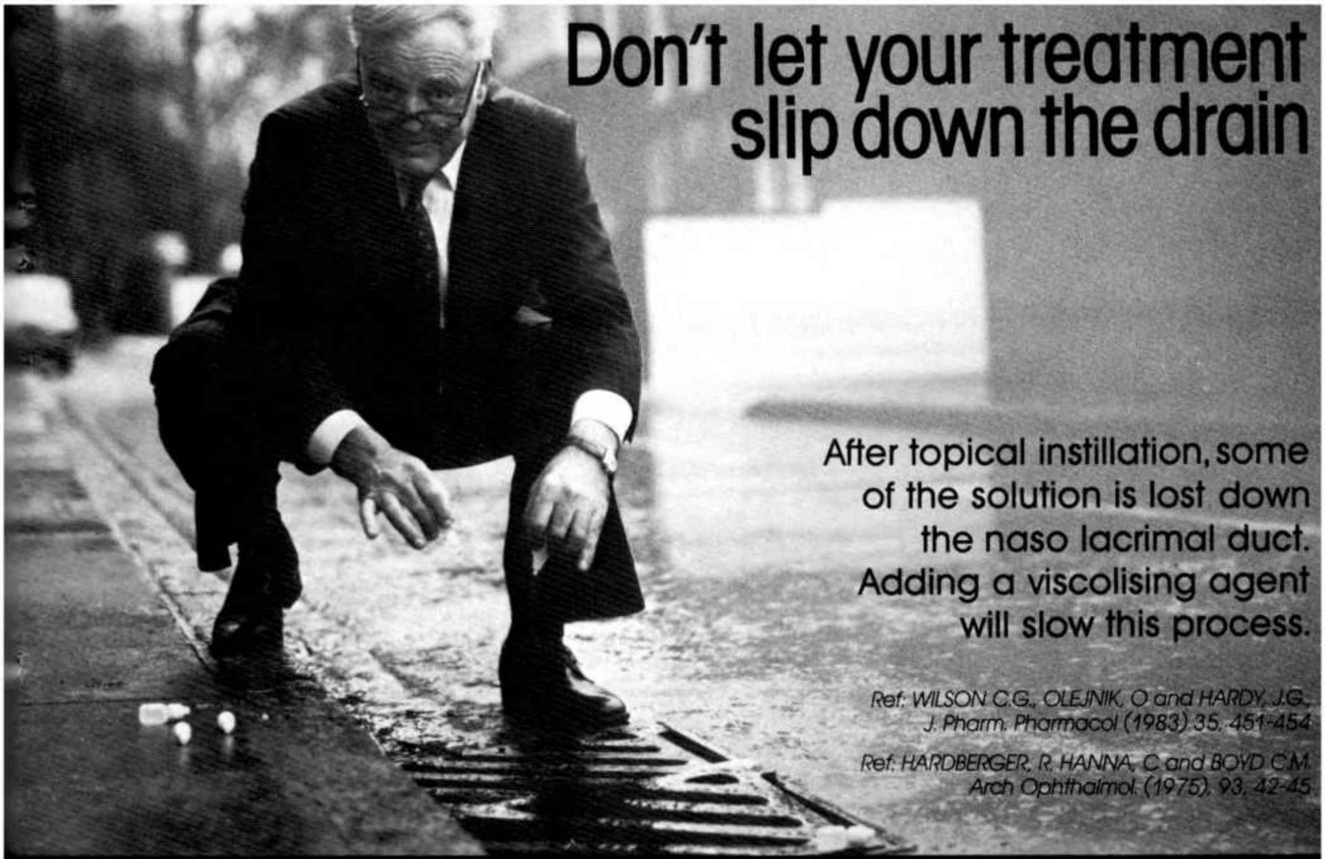

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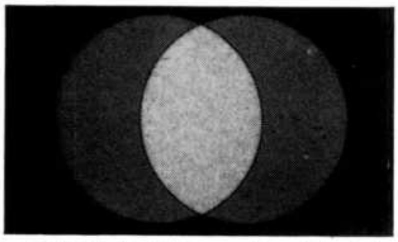

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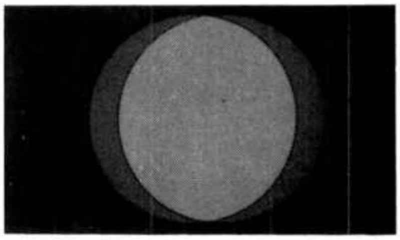

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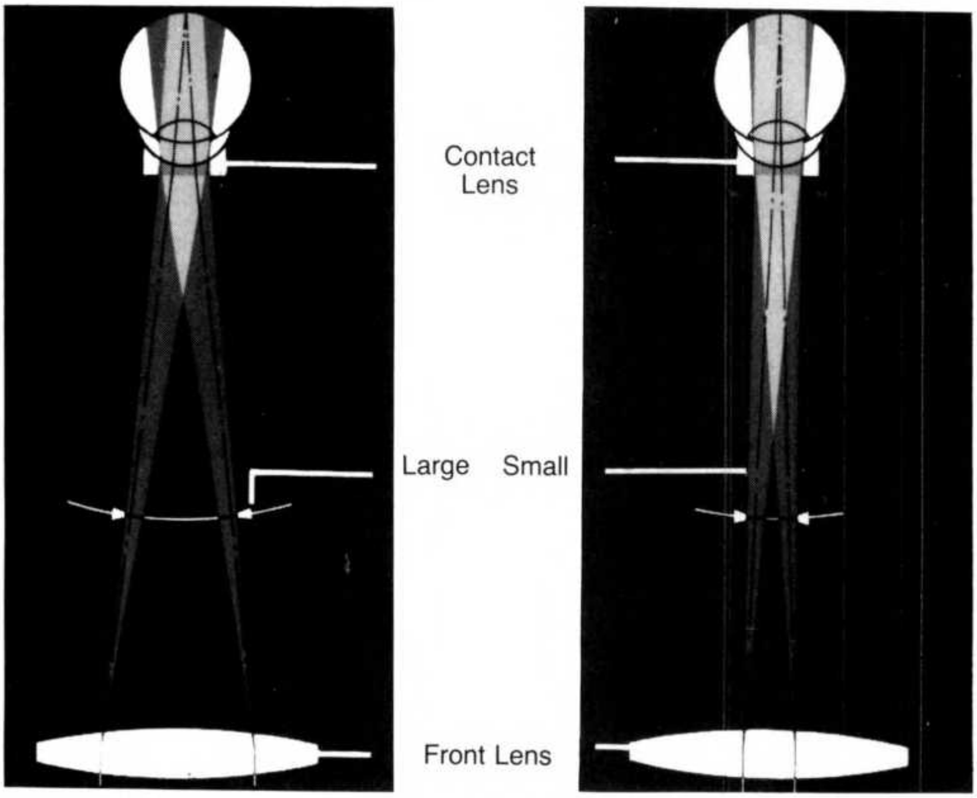

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METHODS

Patient assessment. Diagnosis of AAU was in all cases made by slit-lamp biomicroscope examination and details recorded. Patients were questioned about non-ocular symptoms. In each case a venous blood sample was taken at presentation for HLA typing and assay for antibodies to yersinia. In 21 patients a second blood sample was taken after seven or more days (group 1), leaving 33 patients in whom only acute phase samples were taken (group 2). More wide ranging investigations were later performed on selected patients as indicated: in particular, sacroiliac or other joint *x*-rays were performed if joint symptoms or signs developed.

Serology. All blood samples were assayed for antibodies to *Y. enterocolitica* serotypes 0:3 and 0:9, and *Y. pseudotuberculosis* I to V, the principal pathogenic serotypes in Europe. Titres were measured by tube saline agglutination tests on serum. This test detects IgM and agglutinating IgG antibodies, both of which are present in the acute and early convalescent phases of yersinia infection.[11] Control cultures, antisera, and a protocol for serological testing were kindly supplied by the Yersinia Reference Laboratory, Leicester. Single high titres or a four-fold rise in titre were considered evidence of yersinia infection.

Results

The clinical features of patients in group 1 (with sequential samples) and group 2 (with acute phase samples only) are shown in Table 1. Thirty of the total of 54 patients, including all 13 patients with yersiniosis, were HLA-B27 positive.

Group 1. Seven of the 21 patients who underwent sequential sampling had serological evidence of yersinia infection. *Y. enterocolitica* 0:3 was the most common serotype. Patients with higher titres tended to develop more non-ocular abnormalities, particularly arthritis. It is consistent with previous reports that yersinia antibody titres are higher in patients with joint involvement.[12]

Group 2. Yersiniosis was diagnosed in six of the patients who had acute phase sampling only More varied serotypes were identified in this group. Titres were lower than in group 1, but rising titres would be expected if sequential blood samples had been taken Ocular inflammation was the only evidence of disease in these patients, and this may have been a reason for poorer compliance with follow-up.

In patients who had yersiniosis the clinical features of AAU were similar regardless of species or titres. Unilateral severe AAU was the rule, with visual acuity markedly reduced as with all HLA-B27 patients. No patients had mutton fat keratic precipitates or secondary ocular hypertension. There was marked protein extravasation in the aqueous in 10, posterior synechiae in nine, and anterior vitritis in seven of the 13 cases In addition to topical therapy, subconjunctival corticosteroid and a mydriatic were required in 11 cases and oral corticosteroid in four. Uveitis resolved in all cases after treatment. Visual acuity improved to normal in all except patient number 7 Recurrence of AAU was seen in six cases, sometimes alternating to the fellow eye In patient 7 secondary cataract developed which required extraction.

Five yersiniosis patients proceeded to develop non-ocular symptoms (arthralgia with or without diarrhoea or dysuria), in all cases within weeks of presentation (see Table 1). Joint symptoms developed in all five and sacroiliac joint *x*-rays were performed on these. Sacroiliitis was radiologically confirmed in three; knee and ankle effusions occur-

Table 1 *Anti-yersinia antibodies and clinical features in 13 patients with AAU after yersinia infection Patients 8–13 had only acute phase blood samples taken*

Patient	*Age*	*Sex*	*Yersinia serotype*	*Maximum titre*	*Diarrhoea*	*Arthritis*	*Urethritis*
1	23	M	*pseudotuberculosis* III	160	–	–	–
2	28	F	*enterocolitica* 0 3	320	–	+	+
3	34	M	*enterocolitica* 0 3	320	–	+	–
4	29	M	*pseudotuberculosis* IV	320	–	+	+
5	22	M	*enterocolitica* 0.3	640	+	+	–
6	37	M	*enterocolitica* 0:3	>1280	+	+	+
7	45	M	*enterocolitica* 0·3	160	–	–	–
8	29	F	*enterocolitica* 0.3	80	–	–	–
9	30	F	*pseudotuberculosis* II	160	–	–	–
10	23	M	*pseudotuberculosis* IV	160	–	–	–
11	24	F	*pseudotuberculosis* III	160	–	–	–
12	43	M	*enterocolitica* 0 9	80	–	–	–
13	20	F	*enterocolitica* 0·3	80	–	–	–

red in the other two patients. Urethritis occurred in three patients, in whom chlamydia was excluded as the cause.

Sarcoidosis was later diagnosed in two patients who were yersinia-negative. Brucellosis was diagnosed in one patient whose acute-phase specimen contained antibodies to *Y. enterocolitica* 0.9 in titre 1:320. This cross reaction is well described.[13] Subsequent sampling gave negative results for yersinia and brucella agglutinating titres of 1:1280.

Two members of the control population had titres to *Y pseudotuberculosis* IV of 1:160. The remaining 118 were negative to all yersinia serotypes tested.

Discussion

This study has shown that a considerable proportion (24%) of patients who presented with an apparently idiopathic first attack of AAU had serological evidence of yersinia infection. Joint disease was the most common non-ocular consequence of infection, later becoming evident in five of the 13 patients with yersiniosis. Higher titres of antibody to yersinia were noted in this group.

Two retrospective studies from Finland reported a total of 45 cases of AAU; 42 of these followed *Y. enterocolitica* infection and three followed *Y. pseudotuberculosis*.[6 7] In contrast, AAU was associated with antibodies to *Y. pseudotuberculosis* in five of the 13 yersiniosis patients in this study This reflects the relatively high reported incidence in Dublin of infection with this pathogen [10]

Reiter's syndrome follows genital infection, and the classical triad of urethritis, arthritis, and ocular inflammation is frequently incomplete. Similar arthritis developing in association with gastrointestinal infection is termed 'reactive arthritis'. More than 23 named organisms have been convincingly implicated in reactive arthritis, including *Y enterocolitica* and *Y. pseudotuberculosis*.[14 15] Association with HLA-B27 has been confirmed in several studies.

Timing of uveitis and arthritis after abdominal disease suggests that some kind of host reaction is involved in pathogenesis. Association with HLA-B27 implies genetic factors Bacterial factors influencing the outcome of infection are serotype and carriage of plasmids (extrachromosomal genetic material) which encode virulence. While these host and bacterial factors can be identified which influence outcome of infection by organisms such as yersinia, a hypothetical model must be discussed to explain the pathogenesis of inflammation. According to the molecular mimicry hypothesis, there is cross reactivity between antigenic determinants on bacteria and the HLA-B27 antigens. A consequence of shared determinants between host and foreign antigens is the production against foreign antigens of antibodies which attack target cells (for example, anterior uvea) bearing self antigens and thereby initiating an inflammatory reaction. Cross reacting antigenic determinants are shared by all enteric organisms isolated from B27-positive patients.[16 17] However, cross reactivity cannot explain why the uveal tract (or sacroiliac joints) are preferentially affected, since B27 is not organ specific. The uveal tract is anatomically an isolated area, relatively inaccessible to microbial infection but accessible to diffusible antibodies from the circulation. If target tissue in the uveal tract has molecular structures similar to those on microbes cross reacting with HLA-B27, then perhaps uveitis could be induced.

In a follow-up period of more than one year in most cases we have found inflammation to be confined to the eye in eight of 13 yersiniosis cases. This emphasises that a complete reactive arthritis syndrome is unusual in AAU following yersinia infection, a fact apparent in another series.[7] Acute anterior uveitis following yersinia infection may manifest independently of joint, gastrointestinal, or urethral symptoms. However, these allied abnormalities may be subclinical rather than absent. Intestinal inflammation has been histopathologically confirmed in 67% of reactive arthritis patients, 73% of whom had no symptoms.[18] Similarly, eye inflammation may be subclinical in patients who have clinically evident inflammation elsewhere due to yersinia or similar infection. In other cases the opposite may be true, with eye inflammation dominating the clinical picture.

In recruitment of AAU patients for this study we selected patients who would probably not otherwise be investigated or in whom investigation would not yield a definitive diagnosis. The significant number of these patients with yersinia infection has prompted this report. While it may indicate unusually high prevalence of yersiniosis in Ireland, it is likely that the condition is underdiagnosed by ophthalmologists outside Scandinavia.

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Index to volume 72, 1988

AUTHOR INDEX

Abbuhl, M. F.: *see* Grossniklaus, H. E., etc 212
Abrahamsson, M., and **Sjöstrand, J.:** Contrast sensitivity and acuity relationship in strabismic and anisometropic amblyopia 44
——, **Fabian, G.,** and **Sjöstrand, J.:** Changes in astigmatism between the ages of 1 and 4 years: a longitudinal study 145
Abramson, D. H.: *see* Adams, K. S., etc. 494
Acheson, J. F., McHugh, J. D., and **Falcon, M. G.:** Changing patterns of early complications in cataract surgery with new techniques: a surgical audit 481
Acheson, R. W.: *see* Talbot, J. F., etc 727
Adams, K. S., Abramson, D. H., Ellsworth, R. M., Haik, B. G., Bedford, M., Packer, S., Seddon, J., Albert, D., and **Polivogianis, L.:** Cobalt plaque versus enucleation for uveal melanoma: comparison of survival rates 494
Afshar, F.: *see* Thomas, D. J. B., etc. 299
Aitken, D.: *see* Foulds, W. S., etc. 278
Akbatur, H.: *see* Hasanreisoğlu, B., etc. 139
Albert, D.: *see* Adams, K. S., etc. 494
Albert, D. M.: *see* Alfonso, E., etc. 338
——: *see* Cannistra, A. J., etc. 380
Aldington, S. J.: *see* Mohan, R., etc 841
Alexander, R. A.: *see* Lyness, R. W., etc. 104
Alfonso, E., Arrellanes, L., Boruchoff, S. A., Ormerod, L. D., and **Albert, D. M.:** Idiopathic bilateral lipid keratopathy 338
Alfrich, S. J.: *see* Badenoch, P. R., etc 225
Allam, B.: *see* Karcioğlu, Z. A., etc 793
Alvarez, E., Damato, B. E., Jay, J. L., and **McClure, E.:** Comparative evaluation of oculokinetic perimetry and conventional perimetry in glaucoma 258
Annuar, N. M.: *see* Singh, M., etc. 131
Apt, L.: *see* Singer, T. R., etc 448
Arne, J. L.: *see* Mathis, A., etc. 313
Arrellanes, L.: *see* Alfonso, E., etc. 338
Asbell, P. A.: *see* Serle, J. B., etc. 274
Azadian, B. S.: *see* Stone, S. P., etc. 167
Aziz, M. A.: *see* Newland, H. S., etc. 561
Azuma, I.: *see* Goh, Y., etc. 461

Baarsma, G. S.: *see* La Hey, E., etc 921
Bacon, P., Spalton, D. J., and **Smith, S. E.:** Blindness from quinine toxicity 219
Badeeb, P., Trope, G. E., and **Mortimer, C.:** Short-term effects of neodymium-YAG transscleral cyclocoagulation in patients with uncontrolled glaucoma 615
Badenoch, P. R., Alfrich, S. J., Wedding, T. R., and **Coster, D. J.:** Effectiveness of a decontamination method for donor corneas 225
Bagegni, A., Lyness, R. W., Johnston, P. B., and **Douglas, J. F.:** Visual recovery in orbital vasculitis 737
Baranyovits, P. R.: Stabilisation of refraction following cataract surgery 815
Barber, J. C.: *see* Schulman, J. A., etc. 171
Barber, K., and **Dabbs, T.:** Morphological observations on patients with presumed trichiasis 17
Basu, P. K.: *see* Rootman, D. S., etc 545
Bates, A. K., and **Cheng, H.:** Bullous keratopathy: a study of endothelial cell morphology in patients undergoing cataract surgery 409
Bec, P.: *see* Malecaze F., etc 309
——: *see* Mathis, A., etc. 313
Bedford, M.: *see* Adams, K. S., etc. 494
Bendig, J.: *see* Stone, S. P., etc. 167
Benjamin, L.: The 'poor man's' Landers lens 796
Berger, T.: *see* Bergin, D. J., etc. 863
Bergin, D. J., McCord, C. D., Berger, T., Friedberg, H., and **Waterhouse, W.:** Blepharoclasis 863
Bessières, M. H.: *see* Malecaze, F., etc. 309
——: *see* Mathis, A., etc 313
Billson, F. A.: *see* Dunlop, I. S., etc. 127
Bird, A. C.: *see* Chuang, E. L., etc 918
——: *see* Talbot, J. F., etc. 727
Blach, R. K.: *see* Graham, C. M., etc 434
Bogaerts, J.: *see* Lepage, P., etc. 518
Boniuk, M.: *see* Ferry, A. P., etc. 55
Boruchoff, S. A.: *see* Alfonso, E., etc. 338
Bosniak, S. L.: *see* Rodriguez-Sains, R. S., etc 134
Bovey, E. H.: *see* Buchi, E. R., etc. 239
Bradbury, J. A., Rennie, I. G., and **Parsons, M.:** Adrenaline dacryolith: detection by ultrasound examination of the nasolacrimal duct 935
Brazier, D. J., and **Smith, S. E.:** Ocular and cardiovascular response to topical carteolol 2% and timolol 0·5% in healthy volunteers 101
Brinchmann-Hansen, O., Dahl-Jørgensen, K., Hanssen, K. F., and **Sandvik, L.:** Effects of intensified insulin treatment on retinal vessels in diabetic patients 666
Brittain, G. P. H.: Retinal burns caused by exposure to MIG-welding arcs: report of two cases 570
Broersma, L.: *see* La Hey, E., etc 921
Bron, A. J.: *see* Brown, N. A. P., etc. 538
Brooks, A. M. V., and **Gillies, W. E.:** Blood groups as genetic markers in glaucoma 270
Brown, C. A.: Incontinentia pigmenti: the development of pseudoglioma 452
Brown, N. A. P., and **Sparrow, J. M.:** Control of astigmatism in cataract surgery 487
——, ——, and **Bron, A. J.:** Central compaction in the process of lens growth as indicated by lamellar cataract 538
Bucher, P. J. M., and **IJsselmuiden, C. B.:** Prevalence and causes of blindness in the Northern Transvaal 721
Büchi, E. R., Bovey, E. H., Michel, A. E., Erard, P. A., and **Chave, J.-P.** (*Correspondence*). Can AZT treatment in AIDS patients aggravate pre-existing CMV retinitis? 239
Burd, E. M.: *see* Taylor, P. B., etc. 206
de Bustros, S., Thompson, J. T., Michels, R. G., Rice, T. A., and **Glaser, B. M.:** Vitrectomy for idiopathic epiretinal membranes causing macular pucker 692
Butler, L. (*Correspondence*): Chemical burns to the eye 640

Cafferkey, M. T.: *see* Larkin, D. F. P., etc. 938
Canning, C. R., and **Hague, S.:** Ocular quinine toxicity 23
——, and **Hungerford, J.:** Familial uveal melanoma 241
——, **McCartney, A. C. E.,** and **Hungerford, J.:** Medulloepithelioma (diktyoma) 764

Cannistra, A. J., Albert, D. M., Frambach, D. A., Dreher, R. J., and Roberts, L.: Sudden visual loss associated with clostridial bacteraemia 380
Carnevali, L., Trimarchi, F., Rosso, R., and Stringa, M.: Haemangiopericytoma of the lacrimal sac: a case report 782
Carpenter, G. C.: *see* Shields, C. L., etc 424
Carr, N. J.: *see* Ham, J. A., etc 868
Castle, J.: *see* Teich, S. A., etc 293
Cederberg, D. M.: *see* Orellana, J., etc 525
Chan, Chi-Chao: *see* Wetzig, R. P., etc. 5
Chana, H. S., and Klauss, V.: Crouzon's craniofacial dysostosis in Kenya 196
Char, D. H., Ljung, B.-M., Deschênes, J., and Miller, T. R.: Intraocular lymphoma: immunological and cytological analysis 905
Char, D. H.: *see* Deschênes, J., etc. 83
——: *see* Fries, P. D., etc. 871
Charles, M. W. (*Correspondence*): Revision of ICRP report on reference man 400
Charlesworth, M. C.: *see* Thomas, D. J. B., etc. 299
Charteris, D. G.: Posterior penetrating injury of the orbit with retained foreign body 432
Chave, J.-P.: *see* Buchi, E. R., etc 239
Chayapum, P.: *see* Shuangshoti, S., etc. 713
Chen, V.: *see* Zborowski-Gutman, L., etc 142
Cheng, H.: *see* Bates, A. K., etc 409
——: *see* Vernon, S. A., etc. 401
Chuang, E. L., and Bird, A. C.: Bilaterality of tears of the retinal pigment epithelium 918
Claque, C., Lewkowicz-Moss, S., and Easty, D.: Epithelial cyst in the anterior chamber after penetrating keratoplasty: a rare complication 36
——, **Menage, M. J., and Easty, D. L.:** Severe herpetic keratitis I: Prevalence of visual impairment in a clinic population 530
Clarke, J. R., and Spalton, D. J.: Treatment of senile entropion with botulinum toxin 361
Clifford-Rose, F.: *see* Stone, S. P., etc. 167
Coats, M.: *see* Schulman, J. A., etc 171
Cochran, A. J., Holland, G. N., Saxton, R. E., Damato, B. E., Foulds, W. R., Herschman, H. R., Foos, R. Y., Straatsma, B. R., and Lee, W. R.: Detection and quantification of S-100 protein in ocular tissues and fluids from patients with intraocular melanoma 874
Cole, M. D., and Smerdon, D.: Perforating eye injuries caused by darts 511
——, **Hay, A., and Eagling, E. M.:** Cyclic esotropia in a patient with unilateral traumatic aphakia: case report 305
Collin, J. R. O.: *see* Lyness, R. W., etc 104
Cook, H. T., and Stafford, N. D.: Angiolymphoid hyperplasia with eosinophilia involving the lacrimal gland 710
Cooling, R. J.: *see* Dart, J. K., etc. 326
Coster, D. J.: *see* Badenoch, P. R., etc. 225
Craft, A. W.: *see* Wood, C. M., etc 631

Dabbs, T.: *see* Barber, K., etc 17
Dahl-Jorgensen, K.: *see* Brinchmann-Hansen, O., etc. 666
Dalkos, G. L., Pulido, J., Kathpalia, S. B., and Jackson, G. G.: Intravenous and intraocular ganciclovir for CMV retinitis in patients with AIDS or chemotherapeutic immunosuppression 521
Damato, B. E.: *see* Alvarez, E., etc 258
——: *see* Cochran, A. J., etc. 874
D'Anna, S. A.: *see* Newland, H. S., etc. 561
Darougar, S., and Viswalingham, N. D.: Marginal corneal abscess associated with adult chlamydial ophthalmia 774
——: *see* Monnickendam, M. A., etc. 879
Dart, J. K., Marsh, R. J., Garner, A., and Cooling, R. J.: Fluorescein angiography of anterior uveal melanocytic tumours 326
Dart, J. K. G.: Predisposing factors in microbial keratitis: the significance of contact lens wear 926
Daunius, C.: *see* Seregard, S., etc. 244
David, R.: *see* Rosenblat, I., etc 160
Davies, E. G.: *see* Humphry, R. C., etc. 406
Delleman, J. W.: *see* de Jong, P. T. V. M., etc 439
Deller, M.: Why should surgery for early-onset strabismus be postponed? 110
Deschênes, J., Char, D. H., and Kaleta, S.: Activated T lymphocytes in uveitis 83
——: *see* Char, D. H., etc. 905
De Silva, D. B. K.: *see* Harendra de Silva, D. G., etc 62
Dick, D. J., Newman, P. K., Richardson, J., Wilkinson, R., and Morley, A. R.: Acute posterior multifocal placoid pigment epitheliopathy and sarcoidosis 74
Dilly, N.: *see* Thomson, G. M., etc 399
Dixon, A.: *see* Pe'er, J., etc. 183
Docherty, P. T. C.: A modified irrigating-aspirating needle 368
Doughty, D.: *see* Harnett, A. N., etc. 289
Douglas, J. F.: *see* Bagegni, A., etc. 737
Drake, M. V.: *see* Hoskins, H. D., etc. 591
Draper, G. J.: *see* Sanders, B. M., etc. 576
Dreher, R. J.: *see* Cannistra, A. J., etc 380
Duff, G. R., and Graham, P. A.: A double-cross-over trial comparing the effects of topical carteolol and placebo on intraocular pressure 27
——, **and Newcombe, R. G.:** The 12-hour control of intraocular pressure on carteolol 2% twice daily 890
Dumonde, D. C.: *see* Stanford, M. R., etc 442
Dunlop, C.: *see* Neill, R. A., etc 759
Dunlop, D. B.: *see* Neill, R. A., etc 759
Dunlop, I. A., and Billson, F. A.: Visual failure in allergic aspergillus sinusitis 127
Dunlop, P.: *see* Neill, R. A., etc. 759
Dutton, G. N.: *see* Zeki, S. M., etc 837
Duvall, J.: *see* Patel, B., etc. 550

Eagle, R. C.: *see* Weisenthal, R., etc 248
Eagling, E. M.: *see* Cole, M. D., etc 305
Easty, D.: *see* Claque, C., etc. 36, 530
Elkington, A. R.: *see* Khaw, P. T., etc 473
Ellis, P. P.: *see* Patchett, R. B., etc 377
Ellsworth, R. M.: *see* Adams, K. S., etc 494
Erard, P. A.: *see* Buchi, E. R., etc 239
Esakowitz, L., and Yates, J. R. W.: Congenital corneal anaesthesia and the MURCS association: a case report 236
Eustace, P.: *see* Larkin, D. F. P., etc. 938

Fabian, G.: *see* Abrahamsson, M., etc 145
Falcon, M. G.: *see* Acheson, J. F., etc. 481
——: *see* James, C. B., etc 628
Farhi, D. C.: *see* Grossniklaus, H. E., etc. 212
Fearnley, I. R., Spalton, D. J., Ward, A. M., Slavin, B., and Muncey, F.: α_1-Antitrypsin phenotypes in acute anterior uveitis 636
Feldon, S. T.: *see* Hellin, E. S., etc 674, 678, 683
Fenelon, B.: *see* Neill, R. A., etc 759
Ferry, A. P., Font, R. L., Weinberg, R. S., Boniuk, M., and Schaffer, C. L.: Nocardial endophthalmitis: report of two cases studied histopathologically 55

Ficker, L., Vafidis, G., While, A., and **Leaver, P.:** Long-term follow-up of a prospective trial of argon laser photocoagulation in the treatment of central serous retinopathy 829
Ficker, L. A., Meredith, T. A., Wilson, L. A., and **Kaplan, H. J.:** Role of vitrectomy in *Staphylococcus epidermidis* endophthalmitis 386
Fielder, A. R.: *see* Moseley, M J, etc 50
Fine, B. S.: *see* Pe'er, J., etc. 183
Fine, S. L.: *see* Jost, B F, etc. 11
Findler, G.: *see* Zborowski-Gutman, L., etc 142
Fink, A. I., Jordan, A. J., Lao, P. N., and **Fong, D. A.:** Therapeutic limitations of argon laser trabeculoplasty 263
Fitzke, F. E.: *see* Holden, A. L, etc. 228
Fleutiaux, S.: *see* Malecaze, F., etc 309
Fong, D. A.: *see* Fink, A. I., etc 263
Font, R. L.: *see* Ferry, A. P, etc 55
Foos, R. Y.: *see* Cochran, A. J, etc 874
Foulds, W. S., Aitken, D., and **Lee, W. R.:** Experimental suprachoroidal plombage with a urethane based hydrophilic polymer 278
——. *see* Cochran, A. J., etc. 874
Fowler, S: *see* Stein, J F, etc 162
Frambach, D. A.: *see* Cannistra, A. J., etc. 380
Frayer, W. C.: *see* Weisenthal, R, etc. 248
Friedberg, H.: *see* Bergin, D J, etc. 863
Friedman, A. H.: *see* Mindel, J S, etc 584
——: *see* Teich, S. A, etc. 293
Fries, P. D., and **Char, D. H.:** Bilateral orbital cavernous haemangiomas 871

Galton, D. J.: *see* Thomas, D J B, etc. 299
Garner, A.: *see* Dart, J K., etc. 326
—— *see* Lane, C. M., etc 912
—— *see* Lyness, R. W., etc. 104
—— *see* Taylor, C. M, etc 2
Geyer, O., Lazar, M., Novak, G. D., Shen, D., and **Yeto, C.:** Levobunolol compared with timolol. a four-year study 892
Ghosh, B.: *see* Gupta, A. K., etc. 390
Gibbens, M. V.: Sympathetic influences on the consensual ophthalmotonic reaction 750
——: The consensual ophthalmotonic reaction 746
Gillies, W. R.: *see* Brooks, A M. V., etc 270
Giuffrè, G.: Changing fluorescein angiographic appearance of a subretinal membrane 835
Gjötterberg, M., and **Ingemansson, S. O.:** Intraocular infestation by the reindeer warble fly larva an unusual indication for acute vitrectomy 420
Glaser, B. M.: *see* De Bustros, S, etc. 692
Goh, Y., Nakajima, M., Azuma, I., and **Hayaishi, O.:** Prostaglandin D_2 reduces intraocular pressure 461
Gomez, D. S.: *see* Ormerod, L D., etc 155
Gonnering, R. S.: Extratarsal chalazia 202
Graham, C. M., and **Blach, R. K.:** Indomethacin retinopathy: case report and review 434
Graham, E: *see* Stanford, M. R., etc 442
Graham, P. A.: *see* Duff, G R., etc. 27
Greene, B. M.: *see* Newland, H. S, etc 561
Grey, R. H. B., and **Morris, A.** (*Correspondence*): Ophthalmic survey of a diabetic clinic 160
Grierson, I.: *see* Hitchins, C. A., etc. 498
——: *see* Jiang, D. Y., etc 116
Grossman, S. A., and **Peyman, G. A.:** Long-term visual results after pars plicata lensectomy-vitrectomy for congenital cataracts 601
Grossniklaus, H. E., Farhi, D. C., Jacobson, B. R., and **Abbuhl, M. F.:** Malignant lymphoma of the conjunctiva following Hodgkin's disease 212
Grunwald, J. E., Riva, C. E., and **Kozart, D. M.:** Retinal circulation during a spontaneous rise of intraocular pressure 754
Gulab, A.: *see* Khan, M D, etc 41
Gupta, A. K., Sarin, G. S., Mathur, M. D., and **Ghosh, B.:** A_1-Antitrypsin and serum albumin in tear fluids in acute adenovirus conjunctivitis 390
Gupta, S. K.: *see* Mohan, M, etc 192
Gutman, L: *see* Zborowski-Gutman, L, etc. 142

Hague, S.: *see* Canning, C R, etc 23
——. *see* Thomson, G. M, etc 399
Haik, B. G.: *see* Adams, K S, etc. 494
Hakim, J.: *see* Stone, S P, etc 167
Hallin, E. S., and **Feldon, S. T.:** Graves' ophthalmopathy I. Simple CT estimates of extraocular muscle volume 674
—— and —— Graves' ophthalmopathy. II Correlation of clinical signs with measures derived from computed tomography 678
——, ——, and **Luttrell, J.:** Graves' ophthalmopathy III. Effect of transantral orbital decompression on optic neuropathy 683
Halliday, B. L.: A new surgical head rest 284
Ham, J. A., and **Carr, N. J.:** Testicular cancer presenting as a red swollen lid 868
Hanaskai, K.: *see* Nishi, O, etc 68
Handwerger, S.: *see* Orellana, J., etc 525
Hanssen, K. F.: *see* Brinchmann-Hansen, O., etc 666
Harding, J. J., and **Van Heyningen, R.:** Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide 809
——: *see* Van Heyningen, R, etc 804
Harendra de Silva, D. G., and **De Silva, D. B. K.:** Norrie's disease in an Asian family 62
Harnett, A. N., Doughty, D., Hirst, A., and **Plowman, P. N.:** Radiotherapy in benign orbital disease. II Ophthalmic Graves' disease and orbital histiocytosis X 289
——, **Thorpe, P.,** and **Hungerford, J. H.:** Cavernous haemangioma presenting as an orbital mass after enucleation for a choroidal melanoma· case report 618
——· *see* Plowman, P N., etc. 286
Hasanreisoglu, B., Or, M., and **Akbatur, H.:** Neurofibromatosis associated with retinoblastoma 139
Hasany, S. M.: *see* Rootman, D S, etc. 545
Hay, A.: *see* Cole, M D., etc. 305
Hayaishi, O: *see* Goh, Y., etc 461
Henkind, P.: *see* Sherman, M D, etc. 641
Herschman, H. R.: *see* Cochran, A J, etc 874
Hirst, A.: *see* Harnett, A N, etc 289
Hiscott, P. S.: *see* Jiang, D. Y., etc 116
Hitchins, C. A., and **Grierson, I.:** Intravitreal injection of fibroblasts the pathological effects on the ocular tissues of the rabbit following an intravitreal injection of autologous skin fibroblasts 498
Hoare Nairne, J. E. A., Sherwood, D., Jacob, J. S. H., and **Rich, W. J. C. C.:** Single stage insertion of the Molteno tube for glaucoma and modifications to reduce postoperative hypotony 846
Holden, A. L., and **Fitzke, F. E.:** Image size in the fundus: structural evidence for wide-field retinal magnification factor 228
Holland, G. N.: *see* Cochran, A. J., etc. 874
Hope-Ross, M., Travers, S., and **Mooney, D.:** Solar retinopathy following religious rituals 931
Hoskins, H. D., Magee, S. D., Drake, M. V., and **Kidd, M. N.:** Confidence intervals for change in automated visual fields 591

Howe, J. W.: *see* Wood, C M., etc 631
Hoyt, W. F.: *see* Novakovic, P , etc. . . 176
Hugkulstone, C. E., and **Watt, L. L.** (*Correspondence*). Branch retinal arteriolar occlusion with chickenpox 78
Humphry, R. C., **Davies, E. G.**, **Jacob, T. J. C.**, and **Thompson, G. M.**: The Human Anterior Lens Capsule—an attempted chemical deabridement of epithelial cells by ethylenediaminetetracetic acid (EDTA) and trypsin 406
Hungerford, J.: *see* Canning, C R etc . . 241, 764
Hungerford, J. H.: *see* Harnett, A. N. etc . . . 618

Ijsselmuiden, C. B.: *see* Bucher, P. J. M., etc . . . 721
Ilić, B.: *see* Parunović, A., etc . . . 634
Ingemansson, S. O.: *see* Gjotterberg, M., etc . 420
Inoguchi, T.: *see* Yamana, Y., etc. . . 660
Insler, M. S.: *see* Karcıoğlu, Z A , etc. . . 793
Isenberg, S. J.: *see* Singer, T R., etc . . . 448
Ishibashi, T.: *see* Yamana, Y., etc 660

Jackson, G. G.: *see* Daikos, G L., etc 521
Jacob, J. S. H.: *see* Hoare Nairne, J E. A , etc. 846
Jacob, T. J. C.: *see* Humphry, R C., etc 406
Jacobs, N. A., and **Morgan, L. H.**: On the management of retained airgun pellets a survey of 11 orbital cases 97
——, **Steele, C. A.**, and **Mills, K. B.**: Origin of disc new vessels assessed by videofluorography . . . 394
——: *see* Mills, K B., etc. 465, 469
Jacobson, B. R.: *see* Grossniklaus, H. E., etc . 212
Jagger, J. D.: *see* Pearson, R. V., etc. . . . 485
Jain, M. R.: Drug delivery through soft contact lenses 150
James, C. B., **McDonnell, P. J.**, and **Falcon, M. G.**: Infectious crystalline keratopathy 628
James, C. R.: *see* McLeod, D , etc. . . . 413
Jay, J. L. (*Correspondence*). Cardiac side-effects of beta blocker eyedrops 240
——, and **Murray, S. B.**: Early trabeculectomy versus conventional management in primary open angle glaucoma . . . 881
——. *see* Alvarez, E , etc 258
——. *see* Loeffler, K U., etc 29
Jiang, D. Y., **Hiscott, P. S.**, **Grierson, I.**, and **McLeod, D.**: Growth and contractility of cells from fibrocellular epiretinal membranes in primary tissue culture 116
Johnston, P. B., **Maguire, C. J. F.**, and **Logan, W. C.**: Failed retinal surgery caused by intraocular gas injection 322
——: *see* Bagegni, A , etc. . . 737
de **Jong, P. T. V. M.**, and **Delleman, J. W.**: Familial grouped pigmentation of the retinal pigment epithelium 439
Jordan, A. J.: *see* Fink, A. I., etc. . 263
Jost, B. F., **Olk, R. J.**, **Patz, A.**, **Fine, S. L.**, and **Murphy, R. P.**: Anterior segment ischaemia following laser photocoagulation in a patient with systemic lupus erythematosus 11

Kaleta, S.: *see* Deschênes, J., etc. . . . 83
Kalra, P. A., and **Turney, J. H.**: Mesangioproliferative glomerulonephritis associated with retinitis pigmentosa . . . 210
Kalra, V. K.: *see* Mohan, M., etc. . 192
Kaplan, H. J.: *see* Ficker, L. A., etc 386
Karam, J. H.: *see* Mindel, J. S., etc. . . 584
Karcıoğlu, Z. A., **Allam, B.**, and **Insler, M. S.**: Ocular involvement in sinus histiocytosis with massive lymphadenopathy 793
Kasp, E.: *see* Stanford, M R , etc . . . 442
Kathpalia, S. B.: *see* Daikos, G L., etc 521
Kaufman, H. E.: *see* Tamaki, K., etc 370
Kaur, B.: *see* Singh, M., etc. 131
Kean, D.: *see* Martyn, C. N , etc 515
Kelly, S. P., and **Walley, T. J.**: Effect of the calcium antagonist nifedipine on intraocular pressure in normal subjects 216
Kestelyn, P.: *see* Lepage, P , etc . . 518
Keyvan-Larijani, E.: *see* Newland, H S , etc. 561
Khan, M. D., **Kundi, N.**, **Saeed, N.**, **Gulab, A.**, and **Nazeer, A. F.**: Incidence of keratoconus in spring catarrh 41
Kharlamb, A. B.: *see* Mindel, J. S., etc 584
Khaw, P. T., and **Elkington, A. R.**: Slit-lamp photography made easy by a spot metering system 473
Kidd, M. N.: *see* Hoskins, H D , etc. 591
Kijlstra, A.: *see* La Hey, E , etc . 921
Kingston, J. E.: *see* Sanders, B M., etc. . . 576
Kinnear, P. E.: *see* Stone, S. P , etc 167
Kinsella, F. P., and **Mooney, D. J.**: Angioid streaks in beta thalassaemia minor 303
Kissun, R. D.: *see* Taylor, C M , etc . 2
Klauss, V.: *see* Chana, H. S., etc. . . 196
Kobetz, L. E.: *see* Shields, J A , etc . . 456
Kock, E.: *see* Seregard, S., etc . . 244
Kohner, E. M.: *see* Mohan, R., etc. . . 841
Kozart, D. M.: *see* Grunwald, J E., etc. . . 754
Kundi, N.: *see* Khan, M. D., etc 41
Kyle, G. M.: *see* O'Brien, C J , etc. . . . 189

La Hey, E., **Baarsma, G. S.**, **Rothova, A.**, **Broersma, L.**, **Van der Gaag, R.**, and **Kijlstra, A.**: High incidence of corneal epithelium antibodies in Fuchs' heterochromic cyclitis 921
Laidler, P.: *see* Olver, J , etc 552
Lane, C. M., **Wright, J. E.**, and **Garner, A.**: Primary myxoid liposarcoma of the orbit . 912
Lao, P. N.: *see* Fink, A I , etc . . 263
Larkin, D. F. P., **Cafferkey, M. T.**, and **Eustace, P.**: Yersinia-induced uveitis in Ireland 938
Lawrence, L.: *see* Schulman, J A., etc. . . 171
Lazar, M.: *see* Geyer, O , etc. . . 892
Leaver, P.: *see* Ficker, L , etc . . . 829
Lee, W. R.: *see* Cochran, A J , etc . . 874
—— *see* Foulds, W S., etc. . . 278
Lepage, P., **Bogaerts, J.**, **Kestelyn, P.**, and **Meheus, A.**: Single-dose cefotaxime intramuscularly cures gonococcal ophthalmia neonatorum . 518
Leveque, C.: *see* Schulman, J. A., etc 171
Lewkowicz-Moss, S.: *see* Claque, C , etc 36
Ljung, B.-M.: *see* Char, D. H., etc . . 905
Loeffler, K. U., and **Jay, J. L.**: Tissue response to aqueous drainage in a functioning Molteno implant . 29
Logan, W. C.: *see* Johnston, P B., etc . . . 322
Lommatsch, P. K.: *see* Oosterhuis, J. A , etc . . 317
Luttrell, J.: *see* Hallen, E S , etc . . 683
Lyness, R. W., **Collin, J. R. O.**, **Alexander, R. A.**, and **Garner, A.**: Histological appearances of the levator palpebrae superioris muscle in the Marcus Gunn phenomenon 104
——: *see* Bagegni, A., etc. 737

McCartney, A. C. E.: *see* Canning, C R , etc . . 764
McClure, E.: *see* Alvarez, E., etc . . 258
McCord, C. D.: *see* Bergin, D J , etc 863
McDonnell, P. J.: How do general practitioners manage eye disease in the community? 733
——, and **Mayou, B. J.**: Congenital divided naevus of the eyelids 198

——, and **Spalton, D. J.** (*Correspondence*): Surgical corneal clouding 399
—— *see* James, C. B., etc 628
McHugh, J. D.: *see* Acheson, J. F., etc. 481
McLaren, D. S. (*Correspondence*) Post-measles blindness 879
McLaughlin, B.: *see* Taylor, C. M., etc 2
McLean, I. W.: *see* Zimmerman, L. E., etc 558
McLeod, B. K.: Choroidal osteoma presenting in pregnancy, 612
McLeod, D., and James, C. R.: Viscodelamination at the vitreoretinal juncture in severe diabetic eye disease 413
—— *see* Jiang, D. Y., etc 116
Magee, S. D.: *see* Hoskins, H. D., etc. 591
Maguire, C. J. F.: *see* Johnston, F. B., etc 322
Malamud, S. C.: *see* Orellana, J., etc. 525
Malecaze, F., Bessières, M. H., Bec, P., Fleutiaux, S., Mathis, A., and Seguela, J. P.: Immunological analysis of the aqueous humour in candida endophthalmitis I. Experimental study 309
—— *see* Mathis, A., etc. 313
Manschot, W. A., and van Strik, R. (*Correspondence*)· Is radiation a justifiable treatment of choroidal melanoma? 319
——, and —— (*Correspondence*) Irradiation and choroidal melanoma 558
Marsh, R. J.: Argon laser treatment of lipid keratopathy 900
—— *see* Dart, J. K., etc 326
Martyn, C. N., and Kean, D.: The one-and-a-half syndrome Clinical correlation with a pontine lesion demonstrated by nuclear magnetic resonance imaging in a case of multiple sclerosis 515
Mathis, A., Malecaze, F., Bessières, M. H., Arne, J. L., Seguela, J. P., and Bec, P.: Immunological analysis of the aqueous humour in candida endophthalmitis. II. Clinical study 313
——. *see* Malecaze, F., etc 309
Mather, H. M.: *see* Mohan, R., etc 841
Mathur, M. D.: *see* Gupta, A. K., etc 390
Mathur-Wagh, U.: *see* Orellana, J., etc. 525
Maude, G. H.: *see* Talbot, J. M., etc. 727
Mayou, B. J.: *see* McDonnell, P. J., etc. 198
Mazur, D. O.: *see* Wetzig, R. P., etc. 5
Mebeus, A.: *see* Lepage, P., etc 518
Mehra, V., and Minassian, D. C.: A rapid method of grading cataract in epidemiological studies and eye surveys 801
Mehta, H. K.: Spontaneous reformation of upper eyelid 856
Mekki, Q. A., and Turner, P.: Dopamine-2 receptor blockade does not affect the ocular hypotensive action of timolol 598
Menage, M. J.: *see* Claque, C. M. P., etc 530
Meredith, T. A.: *see* Ficker, L. A., etc. 386
Michel, A. E.: *see* Buchi, E. R., etc 239
Michels, R. G.: *see* De Bustros, S., etc 692
Mildvan, D. S.: *see* Orellana, J., etc. 525
Miller, T. R.: *see* Char, D. H., etc. 905
Mills, K. B., and Jacobs, N. A.: A single-blind randomised trial comparing adrenaline 1·0% with dipivalyl epinephrine (Propine) 0·1% in the treatment of open-angle glaucoma and ocular hypertension 465
——, **Jacobs, N. J., and Vogel, R.:** A study of the effects of four concentrations of D-timolol, 0·25% L-timolol, and placebo on intraocular pressure on patients with raised intraocular pressure 469
—— *see* Jacobs, N. A., etc 394
Minassian, D. C.: *see* Mehra, V., etc. 801
Mindel, J. S., Kharlamb, A. B., Friedman, A. H., Karam, J. H., Stone, R. D., and Siegel, I. M.: N-3-pyridylmethyl-n′-*p*-nitrophenylurea ocular toxicity in man and rabbits 584
Minshull, C.: *see* Moseley, M. J., etc. 50
Mitchell, K. W., Wood, C. M., and Howe, J. W.: Pattern visual evoked potentials in hyperthyroidism 534
Mittal, K. K.: *see* Wetzig, R. P., etc. 5
Mohan, M., Gupta, S. K., Kalra, V. K., Vajpayee, R. B., and Sachdev, M. S.: Topical silver sulphadiazine—a new drug for ocular keratomycosis 192
Mohan, R., Kohner, E. M., Aldington, S. J., Nijhar, I., Mohan, V., and Mather, H. M.: Evaluation of a non-mydriatic camera in Indian and European diabetic patients 841
Mohan, V: *see* Mohan, R., etc. 841
Monnickendam, M. A., and Darougar, S. (*Correspondence*): Postmeasles blindness 879
Mooney, D.: *see* Hope-Ross, M., etc. 931
Mooney, D. J.: *see* Kinsella, F. P., etc. 303
Morgan, L. H.: *see* Jacobs, N. A., etc. 97
Morgan, S. J. (*Correspondence*): Chemical burns to the eye 640
Moriarty, B. J.: Childhood blindness in Jamaica 65
—— *see* Talbot, J. F., etc 727
Morley, A. R.: *see* Dick, D. J., etc 74
Morris, A.: *see* Grey, R. H. B., etc. 160
Mortimer, C.: *see* Badeeb, O., etc 615
Morton, D. B.: *see* Rostron, C. K., etc. 354
Moseley, M. J., Fielder, A. R., Thompson, J. R., Minshull, C., and Price, D.: Grating and recognition acuities of young amblyopes 50
Muncey, F.: *see* Fearnley, I. R., etc. 636
Murphy, R. P.: *see* Jost, B. F., etc. 11
Murray, S. B.: *see* Jay, J. L., etc. 881

Naeser, P.: Optic nerve involvement in a case of methanol poisoning 778
Nakajima, M.: *see* Goh, Y., etc. 461
Nazeer, A. F.: *see* Khan, M. D., etc. 41
Neill, R. A., Dunlop, P., Dunlop, D. B., Fenelon, B., and Dunlop C.: Stereoscopic evoked responses to crossed and uncrossed disparity accompanying simulated refractive error 759
Nelson, L. B.: *see* Shields, C. L., etc. 424
Neumann, R., Zalish, M., and Oliver, M.: Effect of intraocular lens implantation on combined extracapsular cataract extraction with trabeculectomy a comparative study 741
Newcombe, R. G.: *see* Duff, G. R., etc 890
Newland, H. S., White, A. T., Greene, B. M., D'Anna, S. A., Keyvan-Larijani, E., Aziz, M. A., Williams, P. N., and Taylor, H. R.: Effect of single-dose ivermectin therapy on human *Onchocerca volvulus* infection with onchocercal ocular involvement 561
Newman, P. K.: *see* Dick, D. J., etc 74
Ngoc Anh-Le: *see* Serle, J. B., etc. 274
Nichols, C. W.: *see* Weisenthal, R., etc. 248
Nichols, D. A.: *see* Simmons, S. T., etc 688
Nijhar, I.: *see* Mohan, R., etc. 841
Nishi, O., and Hanasaki, K.: Automated morphometry of corneal endothelial cell: use of video camera and video tape recorder 68
Norose, K., Tanino, T., and Segawa, K.: Bilateral tears of the retinal pigment epithelium 621
Novak, G. D.: *see* Geyer, O., etc. 892

Novakovic, P., Taylor, D. S. I., and **Hoyt, W. F.:** Localising patterns of optic nerve hypoplasia—retina to occipital lobe 176
Nussenblatt, R. B.: *see* Wetzig, R. P., etc. 5

O'Brien, C. J., and **Kyle, G. M.:** Metastatic *Staphylococcus aureus* endophthalmitis. a case report 189
Obstbaum, S. A.: *see* Serle, J B , etc 274
Ohnishi, Y.: *see* Yamana, Y , etc. 660
Oka, Y.: *see* Yamana, Y , etc. 660
Oliver, M.: *see* Neumann, R., etc. 741
Olk, R. J.: *see* Jost, B. F , etc. 11
Olver, J., and **Laidler, P.:** Acquired Brown's syndrome in a patient with combined lichen sclerosus et atrophicus and morphoea 552
Olsen, T.: Pre- and postoperative refraction after cataract extraction with implantation of standard power IOL 231
Oosterhuis, J. A., Lommatzsch, P. K., and **Wessing, A.** (*Correspondence*): Is radiation a justifiable treatment of choroidal melanoma? 317
——. *see* Priem, H A , etc. 646
Or, M.: *see* Hasanreisoğlu, B., etc. 139
Orellana, J., Teich, S. A., Winterkorn, J. S., Mathur-Wagh, U., Handwerger, S., Schlamm, H., Malamud, S. C., Yancovitz, S. R., Cederberg, D. M., and **Mildvan, D. S.:** Treatment of cytomegalovirus retinitis with ganciclovir (9-[20hydroxyl-1-(hydroxymethyl) ethoxymethyl] guanine (BW B759U)) 525
——: *see* Rodgers, R , etc 78
——: *see* Teich, S. A , etc. 293
Ormerod, L. D., Gomez, D. S., Schanzlin, D. J., and **Smith, R. E.:** Chronic alcoholism and microbial keratitis 155
——: *see* Alfonso, E , etc. 338

Packer, S.: *see* Adams, K. S., etc. 494
Palestine, A. G.: *see* Wetzig, R. P., etc. 5
Parunović, A., and **Ilić, B.:** Floppy eyelid syndrome associated with keratotorus 634
Patchett, R. B., Wilson, W. B., and **Ellis, P. P.:** Ophthalmic complications with disseminated intravascular coagulation 377
Patel, B., Duvall, J., and **Tullo, A. B.:** Lamellar macular hole associated with idiopathic juxtafoveolar telangiectasia 550
Patz, A.: *see* Jost, B F , etc 11
Pearce, J. L.: *see* Watts, M T., etc 897
Pearson, A. D. J.: *see* Wood, C. M , etc. 631
Pearson, R. V., and **Jagger, J. D.:** The Ciapryna coaxial cannula 485
Pe'er, J., Fine, B. S., Dixon, A., and **Rothberg, D. S.:** Corneal elastosis within lattice dystrophy lesions 183
Penne, R. B.: *see* Simmons, S. T., etc 688
Perkins, E. S.: Depth measurement with the slit-lamp microscope 344
——. Lens thickness in early cataract 348
Peyman, G. A.: *see* Grossman, S. A , etc 601
Plowman, P. N., and **Harnett, A. N.:** Radiotherapy in benign orbital disease. I. Complicated ocular angiomas 286
——. *see* Harnett, A. N etc. 289
Podos, S. M.: *see* Serle, J. B., etc. 274
Polivogianis, L.: *see* Adams, K S , etc. 494
Price, D.: *see* Moseley, M. J., etc. 50
Priem, H. A., and **Oosterhuis, J. A.:** Birdshot chorioretinopathy. clinical characteristics and evolution 646
Prost, M.: Experimental studies on the pathogenesis of retinopathy of prematurity 363
Pulido, J.: *see* Daikos, G L., etc. 521
Rice, T. A.: *see* De Bustros, S , etc 692
Rich, W. J. C. C.: *see* Hoare Nairne, J E. A., etc. 846
Richardson, J.: *see* Dick, D. J., etc. 74
Riddell, P. M.: *see* Stein, J. F., etc 162
Riva, C. E.: *see* Grunwald, J E., etc 754
Robbins, J.: *see* Stanford, M. R , etc 88
Roberts, L.: *see* Cannistra, A J , etc 380
Robins, R.: *see* Rodriguez-Sains, R. S., etc 134
Rodgers, R., and **Orellana, J.** (*Correspondence*): Cranial nerve palsy following retrobulbar anaesthesia 78
Rodriguez-Sains, R. S., Robins, P., Smith, B., and **Bosniak, S. I.:** Radiotherapy of periocular basal cell carcinomas recurrence rates and treatment with special attention to the medial canthus 134
Rootman, D. S., Hasany, S. M., and **Basu, P. K.:** A morphometric study of endothelial cells of human corneas stored in MK media and warmed at 37°C 545
Rose, G. E.: Clinical assessment of retinal elevations: a review of methods and a novel clinical technique 703
Rosenblat, I., David, R., and **Yassur, Y.** (*Correspondence*). Ophthalmic survey of a diabetic clinic 160
Russo, R.: *see* Carnevali, L , etc 782
Rostron, C. K., Sandford-Smith, J. H., and **Morton, D. B.:** Experimental epikeratophakia using tissue lathed at room temperature 354
Rothberg, D. S.: *see* Pe'er, J , etc 183
Rothova, A.: *see* La Hey, E., etc 921
Russell Jones, D., Scoble, I. N., and **Sarkies, N. J. C.:** Intracerebral metastases from ocular melanoma 246

Sachdev, M. S.: *see* Mohan, M., etc 192
Saeed, N.: *see* Khan, M. D , etc. 41
Sanders, B. M., Draper, G. J., and **Kingston, J. E.:** Retinoblastoma in Great Britain 1969–80, incidence, treatment and survival 576
Sanders, M. D.: *see* Stanford, M R , etc. 442
Sandford-Smith, J. H.: *see* Rostron, C. K , etc 354
Sandvik, L. L.: *see* Brinchmann-Hansen, O , etc 666
Sarin, G. S.: *see* Gupta, A. K , etc 390
Sarkies, N. J. C.: *see* Russel Jones, D., etc. 246
Sasaki, T.: *see* Yamabayashi, S., etc. 852
Saxton, R. E.: *see* Cochran, A J , etc 874
Schaffer, C. L.: *see* Ferry, A. P , etc. 55
Schanzlin, D. J.: *see* Ormerod, L D , etc. 155
Schlamm, H.: *see* Orellana, J., etc. 525
Schmitterer, M.: *see* Teich, S A , etc. 293
Schulman, J. A., Leveque, C., Coats, M., Lawrence, L., and **Barber, J. C.:** Fatal disseminated cryptococcosis following intraocular involvement 171
Scoble, I. N.: *see* Russel Jones, D., etc 246
Seddon, J.: *see* Adams, K S , etc 494
Segawa, K.: *see* Norose, K , etc 621
Seguela, J. P.: *see* Malecaze, F., etc 309
——: *see* Mathis, A., etc 313
Seregard, S., Daumlus, C., Kock, E., and **Popovic, V.:** Two cases of primary bilateral malignant melanoma of the choroid 244
Serjeant, G. R.: *see* Talbot, J. F., etc 727
Serle, J. B., Asbell, P. A., Obstbaum, S. A., Podos, S. M., and **Ngoc Anh-Le:** The evaluation of corneal endothelial permeability in PERK study patients 274
Sery, T.: *see* Simmons, S T., etc. 688
Shakin, E. P.: *see* Shields, J A , etc. 456
Sharir, M.: *see* Zborowski-Gutman, L , etc. 142
Shen, D.: *see* Geyer, O., etc 892
Sherman, M. D., and **Henkind, P.:** Photostress recovery in chronic open angle glaucoma 641
Sherwood, D.: *see* Hoare Nairne, J E. A., etc 846

Sherwood, M. B.: *see* Simmons, S. T., etc. 688
Shields, C. L., Nelson, L. B., Carpenter, G. C., and **Shields, J. A.:** Neonatal Graves' disease 424
—— *see* Shields, J. A., etc. 456
Shields, J. A., Shields, C. L., Shakin, E. P., and **Kobetz, L. E.:** Metastasis of choroidal melanoma to the contralateral choroid, orbit, and eyelid 456
——: *see* Shields, C. L., etc. 424
Shuangshoti, S., Chayapum, P., Suwanwela, N., and **Suwanwela, C.:** Unilateral proptosis as a clinical presentation in primary angiosarcoma of skull 713
Siegel, I. M.: *see* Mindel, J. S., etc. 584
Simmons, S. T., Sherwood, M. B., Nichols, D. A., Penne, R. B., Sery, T., and **Spaeth, G. L.:** Pharmacokinetics of a 5-fluorouracil liposomal delivery system 688
Singer, T. R., Isenberg, S. J., and **Apt, L.:** Conjunctival anaerobic and aerobic bacterial flora in paediatric versus adult subjects 448
Singh, M.: Surgery of aphakic retinal detachment 820
——, **Kaur, B.,** and **Annuar, N. M.:** Malignant melanoma of the choroid in a naevus of Ota 131
Siroty, W.: *see* Teich, S. A., etc. 293
Sjöstrand, J.: *see* Abrahamsson, M., etc. 44, 145
Skarf, B.: *see* Woodruff, G., etc. 786
Slavin, B.: *see* Fearnley, I. R., etc. 636
Smerdon, D. L., and **Sutton, G. A.:** Analysis of the factors involved in cosmetic failure following excision of the eye 768
——, and **Willshaw, H. E.:** Visual after-effects associated with the use of high-resolution visual display units 823
——. *see* Cole, M. D., etc. 511
Smith, B.: *see* Rodriguez-Sains, R. S., etc. 134
Smith, R. E.: *see* Ormerod, L. D., etc. 155
Smith, R. J. H. (*Correspondence*): Postmeasles blindness 879
——: Editorial Surgical failure after gas injection 321
——. —— The parallel squint 161
—— ——. Why retrobulbar anaesthesia? 1
Smith, S. E.: *see* Bacon, P., etc. 219
——: *see* Brazier, D. J., etc. 101
Spaeth, G. L.: *see* Simmons, S. T., etc. 688
Spalton, D. J.: Editorial Progress in uveitis 81
—— *see* Bacon, P., etc. 219
——: *see* Clarke, J. R., etc. 361
——. *see* Fearnley, I. R., etc. 636
—— *see* McDonnell, P. J., etc. 399
Sparrow, J. M.: *see* Brown, N. A. P., etc. 487, 538
Stafford, N. D.: *see* Cook, H. T., etc. 710
Stanford, M. R., and **Robbins, J.:** Experimental posterior uveitis. II. Electroretinographic studies 88
——, **Graham, E., Kasp, E., Sanders, M. D.,** and **Dumonde, D. C.:** A longitudinal study of clinical and immunological findings in 52 patients with relapsing retinal vasculitis 442
Steele, C. A.: *see* Jacobs, N. A., etc. 394
Stein, J. F., Riddell, P. M., and **Fowler, S.:** Disordered vergence control in dyslexic children 162
Stone, R. D.: *see* Mindel, J. S., etc. 584
Stone, S. P., Bendig, J., Hakim, J., Kinnear, P. E., Azadian, B. S., and **Clifford-Rose, F.:** Cryptococcal meningitis presenting as uveitis 167
Straatsma, B. R.: *see* Cochran, A. J., etc. 874
Stringa, M.: *see* Carnevali, L., etc. 782
Sutton, G. A.: *see* Smerdon, D. L., etc. 768
Suwanwela, N.: *see* Shuangshoti, S., etc. 713

Tabbara, K. F.: *see* Taylor, P. B., etc. 206
Talbot, J. F., Bird, A. C., Maude, G. H., Acheson, R. W., Moriarty, B. J., and **Serjeant, G. R.:** Sickle cell retinopathy in Jamaican children: further observations from a cohort study 727
Tamaki, K., Varnell, E. D., and **Kaufman, H. E.:** K-Sol corneal preservation at room temperature 370
Tanino, T.: *see* Norose, K., etc. 621
Taylor, C. M., Weiss, J. B., McLaughlin, B., Kissun, R. D., and **Garner, A.:** Increased procollagenase activating angiogenic factor in the vitreous humour of oxygen treated kittens 2
Taylor, D. S. I.: *see* Novakovic, P., etc. 176
Taylor, H. R.: *see* Newland, H. S., etc. 561
Taylor, P. B., Tabbara, K. F., and **Burd, E. M.:** Effect of preoperative fusidic acid on the normal eyelid and conjunctival bacterial flora 206
Teich, S. A., Castle, J., Friedman, A. H., Siroty, W., Orellana, J., and **Schmitterer, M.:** Active cytomegalovirus particles in the eyes of an AIDS patient being treated with 9-[2-hydroxy-1-(hydroxymethyl) ethoxy-methyl]guanine (Ganciclovir) 293
——: *see* Orellana, J. 525
Thomas, D. J. B., Charlesworth, M. C., Afshar, F., and **Galton, D. J.:** Computerised axial tomography and magnetic resonance scanning in the Tolosa-Hunt syndrome 299
Thompson, G. M.: *see* Humphry, R. C., etc. 406
Thompson, J. R.: *see* Moseley, M. J., etc. 50
Thompson, J. T.: *see* De Bustros, S., etc. 692
Thomson, G. M., Dilly, N., and **Hague, S.** (*Correspondence*). Surgical corneal clouding 399
Thomson, I.: Addition of hyaluronidase to lignocaine with adrenaline for retrobulbar anaesthesia in the surgery of senile cataract 700
Thorner, P.: *see* Woodruff, G., etc. 786
Thorpe, P.: *see* Harnett, A. N., etc. 618
Travers, S.: *see* Hope-Ross, M., etc. 931
Trimarchi, F.: *see* Carnevali, L., etc. 782
—— *see* Stringa, M., etc. 782
Trope, G. E.: *see* Badeeb, O., etc. 615
Tsukahara, S.: *see* Yamabayashi, S., etc. 852
Tullo, A. B.: *see* Patel, B., etc. 550
Turner, P.: *see* Mekki, Q. A., etc. 598
Turney, J. H.: *see* Kalra, P. A., etc. 210

Vafidis, G.: *see* Ficker, L., etc. 829
Vajpayee, R. B.: *see* Mohan, M., etc. 192
Van der Gaag, R.: *see* La Hey, E., etc. 921
Van Heyningen, R., and **Harding, J. J.:** A case-control study of cataract in Oxfordshire: some risk factors 804
——: *see* Harding, J. J., etc. 809
Van Strik, R.: *see* Manschot, W. A., etc. 558
Varnell, E. D.: *see* Tamaki, K., etc. 370
Vernon, S. A., and **Cheng, H.:** Panretinal cryotherapy in neovascular disease 401
Viswalingham, N. D.: *see* Darougar, S., etc. 774
Vogel, R.: *see* Mills, K. B., etc. 469

Walley, T. J.: *see* Kelly, S. P., etc. 216
Walters, R.: A fatal case of necrotising fasciitis of the eyelid 428
Ward, A. M.: *see* Fearnley, I. R., etc. 636
Waterhouse, W.: *see* Bergin, D. J., etc. 863
Watt, L. L.: *see* Hugkulstone, C. E., etc. 78
Watts, M. T., and **Pearce, J. L.:** Day-case cataract surgery 897
Weale, R. A.: Corneal shape and astigmatism: with a note on myopia 696
Wedding, T. R.: *see* Badenoch, P. R., etc. 225
Weinberg, R. S.: *see* Ferry, A. P., etc. 55

Weisenthal, R., **Frayer**, W. C., **Nichols**, C. W., and **Eagle**, R. C.: Bilateral ocular disease as the initial presentation of malignant lymphoma 248

Weiss, J. B.: *see* Taylor, C. M., etc. 2

Wessing, A.: *see* Oosterhuis, J. A., etc 317

Wetzig, R. P., **Chan**, **Chi-Chao**, **Nussenblatt**, R. B., **Palestine**, A. G., **Mazur**, D. O., and **Mittal**, K. K.: Clinical and immunopathological studies of pars planitis in a family 5

While, A.: *see* Ficker, L., etc. 829

White, A. T.: *see* Newland, H. S , etc. 561

Wilkinson, R.: *see* Dick, D. J., etc. 74

Williams, P. N.: *see* Newland, H. S., etc. 561

Willshaw, H. E.: *see* Smerdon, D. L., etc 823

Wilson, L. A.: *see* Ficker, L A , etc. 386

Wilson, W. B.: *see* Patchett, R B., etc. 377

Winterkorn, J. S.: *see* Orellana, J , etc. 525

Wood, C. M., **Pearson**, A. D. J., **Craft**, A. W., and **Howe**, J. W.: Globe luxation in histiocytosis X 631

——: *see* Mitchell, K. W., etc. 534

Woodruff, G., **Thorner**, P., and **Skarf**, B.: Primary Ewing's sarcoma of the orbit presenting with visual loss 786

Wright, J. E.: *see* Lane, C M., etc 912

Wykes, W. N.: A 10-year survey of penetrating eye injuries in Gwent, 1976–85 607

Yamabayashi, S., **Yamamoto**, T., **Sasaki**, T., and **Tsukahara**, S.: A case of 'low-tension' glaucoma' with primary empty sella 852

Yamamoto, T.: *see* Yamabayashi, S., etc. 852

Yamana, Y., **Oka**, Y., **Ohnishi**, Y., **Ishibashi**, T., and **Inoguchi**, T.: Reflow of obstructed capillaries in the maculae of humans with diabetic retinopathy, observed by fluorescein angiography 660

Yancovitz, S. R.: *see* Orellana, J , etc 525

Yassur, Y.: *see* Rosenblat, I , etc. 160

Yates, J. R. W.: *see* Esakowitz, L., etc 236

Yeto, C.: *see* Geyer, O., etc. 892

Zalish, M.: *see* Neumann, R , etc. 741

Zborowski-Gutman, L., **Gutman**, I., **Chen**, V., **Sharir**, M., and **Findler**, G.: Acute angle closure glaucoma precipitated by orbital pseudotumour 142

Zeki, S. M., and **Dutton**, G. N.: Photocoagulation of raised new vessels by long-duration low-energy argon laser photocoagulation—a preliminary study 837

Zimmerman, L. E., and **McLean**, I. W. (*Correspondence*). Irradiation and choroidal melanoma 558

British Journal of Ophthalmology, 1988, **72**, 950

SUBJECT INDEX 1988

- **Acuity, visual:**
  - best, prevalence study in severe herpetic keratitis 530
  - contrast sensitivity relationship, in strabismic and anisometropic amblyopia 44
  - grating and recognition, in young amblyopes 50
  - photostress recovery time and, open angle glaucoma and 641
  - in primary open angle glaucoma, early trabeculectomy and 881
  - strabismus and 110
- **Adrenaline:**
  - dacryolith, detection by ultrasound examination of nasolacrimal duct 935
  - 1·0%, Propine 0·1% compared with, in open angle glaucoma and ocular hypertension 465
- **After-effects, visual,** high-resolution visual display units and 823
- **AIDS:**
  - cryptococcosis and 169
  - ganciclovir for CMV retinitis in 521
  - AZT treatment in, aggravation of pre-existing CMV retinitis and 239
  - treatment, ganciclovir, active cytomegalovirus particles in eyes and 293
- **Airgun pellets,** retained, management 97
- **Alcohol,** risk factor for cataract 807, 809
- **Alcoholism,** chronic, microbial keratitis and 155
- **Alphabetical syndromes** 110
- **Amblyopia:**
  - anisometropic, contrast sensitivity and acuity relationship in 44
  - strabismic, contrast sensitivity and acuity relationship in 44
  - unilateral, contrast sensitivity and acuity relationship in 44
  - young people, grating and recognition acuities in 50
- **Ammonia,** differentiation for antipersonnel or anti-rape sprays 640
- **Anaesthesia:**
  - local, in day-case cataract surgery 897
  - retrobulbar: complications 1
    - cranial nerve palsy following 78
    - hyaluronidase added to lignocaine with adrenaline for, in senile cataract surgery 700
    - safety 1
- **Analgesics,** aspirin-like, protection against cataract and 809
- **Angiogenic factor,** procollagenase activating, increase in vitreous, oxygen treatment and, kitten 2
- **Angiography, fluorescein:**
  - anterior uveal melanocytic tumours 326
  - in birdshot chorioretinopathy 651
  - reflow of obstructed capillaries in maculae with diabetic retinopathy and 660
  - retinal pigment epithelial tears 622
  - sickle cell retinopathy 730, 731
  - subretinal membrane, changing appearance 835
  - video-, origin of disc new vessels assessed by 394
- **Angioid streaks,** in beta thalassaemia minor 303
- **Angioma,** ocular, complicated, radiotherapy in 286
- **Angiosarcoma:**
  - primary, skull, unilateral proptosis and 713
  - skull, treatment 713
- **Ankylosing spondylitis,** lymphocyte lysis and 81
- **Anterior chamber:**
  - depth, measurement, with slit-lamp microscope 344
  - epithelial cyst in, after penetrating keratoplasty 36
- **Anterior segment,** ischaemia, following laser photocoagulation in patient with systemic lupus erythematosus 11
- **α_1-Antitrypsin:**
  - level in tear fluids in acute adenovirus conjunctivitis 390
  - phenotypes, in acute anterior uveitis 636
  - uveitis and 81
- **Aphakia:**
  - glasses 721
  - retinal detachment surgery in, prospective study 820
  - traumatic, unilateral, cyclic esotropia in 305
- **Aponeurosis,** tuck, external levator, for atrophic blepharochalasis 863
- **Aqueous humour:**
  - drainage, tissue response to, in functioning Molteno implant 29
  - immunological analysis, in candida endophthalmitis. clinical study 313
    - rabbit 309
  - S-100 protein in, detection and quantification, in intraocular melanoma 874
- **Aspergillus,** sinusitis, allergic, visual failure in 127
- **Astigmatism:**
  - changes between ages of 1 and 4, longitudinal study 145
  - control in cataract surgery 487
  - corneal shape and 696
- **ATP contraction assay,** cells from fibrocellular epiretinal membranes in primary tissue culture 116
- **Autoantibodies,** Fuchs' heterochromic cyclitis and 921
- **Autoradiography,** after intravitreal fibroblast injection (rabbit) 499
- **Awards:**
  - David Cole Travel Fellowship 240, 400
  - Glaucoma Group Research Grant, 240, 400
  - Ludwig von Sallzmann Prize 240
- **AXT,** treatment in AIDS, aggravation of pre-existing CMV retinitis and 239

- **Bacteraemia,** clostridial, sudden visual loss and 380
- **Bacterial flora,** conjunctival, anaerobic and aerobic, adults and children compared 448
- **Ballpoint pen tip,** orbital injury and 432
- **Beer drinking,** heavy, risk factor for cataract 807, 809
- **Betablocker,** eyedrops, cardiac side effects 240
- **Beta thalassaemia minor,** angioid streaks in 303
- **Blepharitis,** management by general practitioners in community 733
- **Blepharochalasis:** 863
  - atrophic, cosmetic surgery for 863
- **Blind/Blindness:**
  - children, Jamaica 65
  - congenital, Norrie's, in Sri Lanka 62
  - painful eye, concealing melanoma 247
  - postmeasles 879
  - prevalence and causes, Northern Transvaal 721
  - quinine toxicity causing 219
- **Blood-aqueous barrier,** subclinical breakdown, after radial keratotomy 274
- **Blood:**
  - groups, genetic markers in glaucoma 270
  - sugar levels, retinal volume flow and, in diabetics 671

Book Reviews:
  Bartholomew, R. S.: A Practical Guide to Cataract and Lens Implant Surgery, 1987 . . . 479
  Bauernfeind, J. C. (Ed.): Vitamin A Deficiency and its Control, 1986 476
  Bruner, W. E., Stark, W. J., Maumenee, A. E. (Eds.): Manual of Corneal Surgery, 1987 640
  Cairns, J. E. (Ed.) Glaucoma. Vols 1 and 2, 1986 478
  Dodd, B. and Campbell, R. (Eds.) Hearing by Eye. The Psychology of Lip-Reading, 1987 . . . 479
  Draeger, J. and Winter, R. (Eds.) New Microsurgical Concepts Posterior and Anterior Segments, 1987 720
  Eagling, E. M. and Roper-Hall, M. J.: Eye Injuries: An Illustrated Guide, 1986 478
  Etienne, R. (Ed.) Glaucomes secondaires Actualités sur le Glaucome. 1986 . . 478
  Gramberg-Danielsen, B. Rechtliche Grundlagen der augenarztlichen Tatigkeit, 1986 477
  Grant, W. M.. Toxicology of the Eye, 1986 . . 480
  Griffith, D. G., Salasche, S. J., Clemons, D. E. Cutaneous Abnormalities of the Eyelid and Face An Atlas with Histopathology, 1987 799
  Hamano, H. and Kaufman, H. E.· The Physiology of the Cornea and Contact Lens Applications, 1986 475
  Karcioğlu, Z. A. (Ed.): Laboratory Diagnosis of Ophthalmology, 1987 478
  Lamberts, D. W. and Potter, D.-E. (Eds.): Clinical Ophthalmic Pharmacology, 1987 . . . 799
  Lim, A. S. M. · Peripheral Iridectomy Surgical, Argon, YAG, 1987 479
  Lund, O.-E. and Waubke, T. N. (Eds.). Bücherei des Augenarztes. Vol. 109. Akute Augenerkrankungen Akute Symptome, 1986 477
  Michaels, D. D. (Ed.) Visual Optics and Refraction· A Clinical Approach, 1985 . . 478
  Miller, S. (Ed.). Clinical Ophthalmology, 1987 . . 477
  Nelson, L. B., Brown, G. C., Arenstein, J. J. Recognizing Patterns of Ocular Childhood Disease, 1985 479
  Reinecke, R. D. (Ed.): Ophthalmology Annual 1987 476
  Reiner, J. Auge und Brille Beitrage zur Optik des Auges und der Brille, 1987 476
  Schwab, L.: Primary Eye Care in Developing Nations, 1987 475
  Shorr, N. and Seiff, S. R.: Cosmetic Blepharoplasty· An Illustrated Surgical Guide, 1986 . . . 477
  Smith, B. C. Ophthalmic Plastic and Reconstructive Surgery. Vols 1 and 2, 1987 . . . 799
  Strempel, I. (Ed.). Complications in Modern Ophthalmic Surgery, 1987 720
  Weinstein, G. W.: Contemporary Issues in Ophthalmology: Open-Angle Glaucoma, 1986 799
Botulinum toxin, in senile entropion treatment . . 361
Brain, posterior fossa, ocular melanoma metastasis and 247
Brown's syndrome, acquired, in combined lichen sclerosus et atrophicus and morphoea 552
Bruch's membrane:
  bilaterality of retinal pigment epithelial tears and . 918
  nocardiosis and 55
Burns, ocular:
  chemical 604
    differentiating ammonia from antipersonnel or antirape sprays in 640

Camera:
  non-mydriatic, evaluation in Indian and European diabetic patients 841
  video, automated corneal endothelial cell morphometry and 68
Cancer, testicular, presenting as red swollen lid . 868
Candida endophthalmitis:
  aqueous, immunological analysis, in. clinical study 313
    rabbit 309
Canthoplasty, lateral, for atrophic blepharochalasis . 863
Carbenicillin, delivery through soft contact lenses . . 150
Carcinoma, basal cell, periocular, radiotherapy, medial canthus and 134
Carteolol:
  cardiac side-effects 240
  topical, intraocular pressure and . . 27
  2%, topical, ocular and cardiovascular response to, in healthy volunteers 101
    12-hour intraocular pressure control and, timolol compared with 890
CAT, *see* Tomography, computed
Cataract:
  congenital, pars plicata lensectomy-vitrectomy for, long-term visual results 601
  drugs acting as risk factors for 809
  early, lens thickness in 348
  extraction. anaesthesia, retrobulbar, and 1
    astigmatism control in 487
    bullous keratopathy and 409
    complications, early, changing patterns with new techniques 481
    cortical cleansing during, Ciapryna coaxial cannula and 485
    day-case 897
    extracapsular experimental epithelial cell debridement by EDTA and trypsin and . . 406
      trabeculectomy combined with, effect of intraocular lens implantation on, comparative study 741
    preoperative fusidic acid, effect on normal lid and conjunctival bacterial flora and . 206
    refraction stabilisation after 815
    standard power IOL implantation and, refraction results after 231
    surgical audit 481
    suture type, stabilisation of refraction and . . 815
  grading, rapid method, in epidemiological studies and eye surveys 801
  lamellar: central compaction in lens growth process indicated by 538
    shape changes during life 538
  population, attributable risk percentages for . . 807
  risk factors in, case-control study in Oxfordshire 804
  senile. blindness due to, Northern Transvaal 721
    surgery, hyaluronidase added to lignocaine with adrenaline for retrobulbar anaesthesia in . . 700
Catarrh, spring, incidence of keratoconus in . . 41
Cefotaxime, intramuscular, for gonococcal ophthalmia neonatorum 518
Chalazion, extratarsal 202
Chemotherapy, retinoblastoma, statistics 579
Chicken-pox, branch retinal arteriolar occlusion with 78
Child/Children:
  blind, Jamaica 65
  blindness in, measles, herpes simplex infection, and vitamin A deficiency, role in 879
  conjunctival anaerobic and aerobic bacterial flora in, adults compared 448
  Jamaican, sickle cell retinopathy in, cohort study . . 727
  newborn, Graves's disease in 424
  Nigerian, postmeasles blindness in . . . 880
  primary Ewing's sarcoma, orbital, with visual loss in 786

- **Chlamydia trachomatis**, ophthalmia due to, marginal corneal abscess and 774
- **Chloramphenicol**, topical, use in general practice 733
- **Chloromycetin**, delivery through soft contact lenses 150
- **Chorioretinopathy**, birdshot, clinical characteristics and evolution 646
- **Choroid/Choroidal:**
  - lesions, depigmented, in birdshot chorioretinopathy 656
  - lymphomatous deposit 249
  - melanoma. enucleation for, cavernous haemangioma presenting as orbital mass after 618
    - justification of radiation in 317, 319
    - malignant: bilateral, primary 244
      - in naevus of Ota 131
    - metastasis to contralateral choroid, orbit and eyelid 456
    - radiotherapy and 558, 559
  - metastasis from contralateral choroidal melanoma 456
  - osteoma in pregnancy 612
  - reaction, to functioning Molteno implant 29
- **Clapryna coaxial cannula,** 485
- **Circulating immune complexes**, in relapsing retinal vasculitis 443
- **Clostridium**, bacteraemia, sudden visual loss and 380
- **Clostridium septicum** panophthalmitis 380
- **Coagulation**, disseminated intravascular, ophthalmic complications 377
- **Cobalt plaques**, enucleation compared with, in uveal melanoma 495
- **Colour:**
  - flow cytometry, T lymphocyte activation in uveitis and 83
  - vision tests, use of high-resolution visual display units and 824
- **Congenital:**
  - corneal anaesthesia, in MURCS association 236
  - divided naevus of lids 198
- **Congresses, Courses, etc:**
  - American Academy of Ophthalmologists, 92nd Annual Meeting, October, 1988, Las Vegas 480
  - Association for Eye Research, 29th meeting, September, 1988, Albena, Bulgaria 480
  - Clinical Ophthalmological Symposium, December, 1988, Hong Kong 640
  - European Ophthalmic Pathology Society, 27th Annual Meeting, Utrecht, June, 1988, report 800
  - X Interamerican course in clinical ophthalmology 240
  - International Conference on Ophthalmic Photography, March, 1990, Singapore 480
  - VIII International Congress of Eye Research, September, 1988, San Francisco 240
  - XXVI International Congress of Ophthalmology, March, 1990, Singapore 240
  - International Congress on Ocular Trauma, February, 1989, Tel Aviv 640
  - I International Ocular Trauma Conference, Chengchow, China, April, 1988 160
  - V International Retinitis Pigmentosa Congress, November, 1988, Melbourne 240, 640
  - International Society of Geographical Ophthalmology, meeting, August, 1988, Nairobi 240
  - VII Intraocular Implantlens Council Meeting, August, 1989, Zurich 640
  - Ophthalmological Society of East Africa, meeting, August, 1988, Nairobi 240
- **Conjunctiva/Conjunctival:**
  - bacterial flora: anaerobic and aerobic, adults and children compared 448
    - normal, preoperative fusidic acid and 206
  - bulbar, mass, in sinus histiocytosis with massive lymphadenopathy 793
  - lymphoma, malignant, after Hodgkin's disease 212
- **Conjunctivitis:**
  - adenovirus, acute, α_1-antitrypsin and serum albumin levels in tear fluids in 390
  - allergic, management by general practitioners in community 733
  - bacterial, management by general practitioners in community 733
- **Contact lenses:**
  - soft, drug delivery through 150
  - wear, significance in microbial keratitis 926
- **Contrast** sensitivity, acuity relationship and, in strabismic and anisometropic amblyopia 44
- **Cornea/Corneal:**
  - anaesthesia, congenital, MURCS association and 236
  - clouding, surgical 399
  - donor, decontamination method for, effectiveness 225
  - dystrophy, lattice, corneal elastosis within 183
  - elastosis, within lattice dystrophy lesions 183
  - endothelium: cell, morphometry, automated, video camera and tape recorder and 68
    - permeability, evaluation in PERK study patients 274
  - epithelium antibodies, high incidence in Fuchs' heterochromic cyclitis 921
  - hydrops: penetrating keratoplasty for, epithelial cyst in anterior chamber after 36
    - spring catarrh and 41
  - margin, abscess, adult chlamydial ophthalmia and 774
  - pH, K-Sol preservation at room temperature and 372
  - preservation, with K-Sol, at room temperature, rabbit 370
  - scarring, trachomatous, blindness due to, Northern Transvaal 721
  - shape, astigmatism and 696
  - storage in MK media, endothelial cell morphometric study and 545
  - thinning, severe, after argon laser treatment of lipid keratopathy 900
  - ulceration, African children, role of vitamin A deficiency, measles and herpes simplex infection in 879
- **Cortex, visual**, separate subsystems for processing crossed and uncrossed disparity in 759
- **Cranial nerve**, palsy, following retrobulbar anaesthesia 78
- **Crouzon's disease**, Kenya 196
- **Critical flicker frequency**, foveal peak, to red, loss with use of high-resolution visual display units 823
- **Cryotherapy**, panretinal, in neovascular disease 401
- **Cryptococcal meningitis**, presenting as uveitis 167
- **Cryptococcosis**, disseminated, fatal, after intraocular involvement 171
- ***Cryptococcus neoformans***, ocular disease and 173
- **CS gas**, ocular burns, differentiation from antirape sprays 640
- **Cüppers's faden operation** 111
- **Cyclitis**, Fuchs' heterochromic, high incidence of corneal epithelium antibodies in 921
- **Cyclocoagulation**, transscleral neodymium-YAG, in uncontrolled glaucoma, short-term effects 615
- **Cyclopenthiazide**, protection against cataract 809
- **Cyclophosphamide**, sudden visual loss with orbital vasculitis in polyarteritis nodosa and 737
- **Cyst**, epithelial, in anterior chamber, after penetrating keratoplasty 36
- **Cytology**, vitreous, intraocular lymphoma and, review 905

Cytomegalovirus:
- particles, active in eyes of AIDS patient on Ganciclovir treatment 293
- retinitis in AIDS or chemotherapeutic immunosuppression, ganciclovir for 521
  - treatment, ganciclovir 525

Dacryocystitis, chronic, in sinus histiocytosis with massive lymphadenopathy 793
Dacryolith, adrenaline, detection by ultrasound examination of nasolacrimal duct 935
Darts, penetrating ocular injuries due to 511, 608
Dermis fat graft, for atrophic blepharochalasis 863
Dermot Pierse Lecture 720
Diabetes:
- clinic, ophthalmic surgery 160
- effects of intensified insulin treatment on retinal vessels in 666
- Indian and European patients, evaluation of non-mydriatic camera in 841
- retinal vessel light reflex and 671

Diarrhoea, severe, risk factor in cataract 804
Diktyoma, diagnosis and treatment 764
Dipivalyl epinephrine, 0·1%, adrenaline 1·0% compared with, in open-angle glaucoma and ocular hypertension 465
Disease, ocular:
- bilateral, initial presentation of malignant lymphoma 248
- diabetic, severe, viscodelamination at vitreoretinal juncture in 413
- management by general practitioners in the community 733

Disparity, crossed and uncrossed, simulated refractive error and, stereoscopic evoked responses to 759
Disseminated intravascular coagulation, ophthalmic complications with 377
Diuretics, risk factor for cataract 809
Dopamine-2 receptor, blockade, ocular hypotensive action of timolol and 598
Drugs, delivery through soft contact lenses 150
D-timolol, effect on raised intraocular pressure 469
Dyslexia:
- disordered vergence control in 162
- failure of vergence to small targets and 161

Dysostosis, craniofacial, Crouzon's, in Kenya 196

EDTA, trypsin and, lens epithelial cell debridement by 406
Editorial:
- Progress in uveitis 81
- Surgical failure after gas injection 321
- The parallel squint 161
- Why retrobulbar anaesthesia? 1

Electron microscopy:
- cells from fibrocellular epiretinal membranes, growth and contactility in primary tissue culture 116
- corneal elastosis within lattic dystrophy lesions and 183
- cytomegalovirus particles in eyes of AIDS patient on Ganciclovir treatment 293
- epikeratophakia with tissue lathed at room temperature and, rabbit 354
- epithelial cyst in anterior chamber after keratoplasty 39
- lid border entropion in trichiasis 17
- orbit, primary Ewing's sarcoma 788
- scanning: corneal endothelial cells preserved in K-Sol, rabbit 372
  - intravitreal fibroblast injection and, rabbit 500
- tissue reaction of functioning Molteno implant and 29
- transmission: corneal endothelial cells preserved in K-Sol, rabbit 372
  - idiopathic bilateral lipid keratopathy and 340
  - intravitreal fibroblast injection and, rabbit 499

Electro-oculography:
- abnormal, in quinine toxicity 25
- blindness due to quinine toxicity and 221
- indomethacin retinopathy and 434

Electroretinography:
- blindness due to quinine toxicity and 221
- changes, PNU rat poison and 584
- findings, quinine toxicity and 25
- indomethacin retinopathy and 434
- optic nerve hypoplasia and 178
- studies in experimental posterior uveitis, rat 88

Endophthalmitis:
- candida: aqueous, immunological analysis, in, clinical study 313
  - rabbit 309
- globe luxation and, in Crouzon's diseases 196
- nocardial, histopathological study 55
- *Staphylococcus aureus*, metastatic 189
- *Staphylococcus epidermidis*, vitrectomy in 386

Entropion:
- lid border, in trichiasis 17
- senile, treatment, botulinum toxin 361
- trichiasis and 17

Enucleation:
- cobalt plaque compared with, in uveal melanoma 495
- for retinoblastoma, statistics 579

Eosinophilia, angiolymphoid hyperplasia and, lacrimal gland and 710
Epidemiology, rapid cataract grading method for 801
Epikeratophakia, tissue lathed at room temperature and, rabbit 354
Epiretinal membranes:
- fibrocellular, growth and contractility of cells from, in primary tissue culture 116
- idiopathic, macular pucker due to, vitrectomy for 692

ESAF, increase in vitreous, oxygen treatment and, kitten 2
Esotropia, cyclic, unilateral traumatic aphakia and 305
Ethyenediaminetetracetic acid, *see* EDTA
Ewing's sarcoma, primary, orbital, visual loss and 786
Exophthalmos:
- angiolymphoid hyperplasia involving lacrimal gland and 710
- extraocular muscle enlargement, in Graves's ophthalmopathy 674

Eye/Eyes:
- excision, cosmetic failure following, factors in, analysis 768
- surveys, rapid cataract grading method for 801

Eye bank, decontamination methods, effectiveness 225
Eyedrops, betablocker, cardiac side effects 240
Eyelashes, metaplastic, Stevens-Johnson syndrome and 21
Eyelid, *see* Lid

Fasciitis, necrotising, fatal, eyelid 428
Fibroblasts, intravitreal injection, rabbit 498
Fibrocellular epiretinal membrane explants, growth and contractility, in primary tissue culture 116
Fields, visual:
- automated, change in, confidence intervals for 591
- changes, in primary open angle glaucoma, classification 882
- 'low tension glaucoma' and primary empty sella and 853

  sudden visual loss with orbital vasculitis in polyarteritis nodosa and 739
Floppy eyelid syndrome, keratotorus and 634
5-Fluorouracil, liposomal delivery system, pharmacokinetics 688
Foreign body, retained, in posterior penetrating orbital injury 432
Fuchs' heterochromic cyclitis, high incidence of corneal epithelium antibodies in 921
Fundus:
  camera, non-mydriatic, evaluation in Indian and European diabetic patients 841
  image size in, wide-field retinal magnification factor and 228
Funduscopy, indirect, in gas-filled phakic eye 796
Fusidic acid, preoperative, effect on normal lid and conjunctival bacterial flora 206

Ganciclovir:
  in cytomegalovirus retinitis 525
  intravenous and intraocular, for CMV retinitis in AIDS or chemotherapeutic immunosuppression 521
  treatment in AIDS, active cytomegalovirus particles in eyes and 293
General practitioners, managing eye disease in community and 733
Genetic markers, blood groups as, in glaucoma 270
Gentamicin:
  antidote to ocular toxicity of PNU 584
  delivery through soft contact lenses 150
Glaucoma:
  angle closure, acute, orbital pseudotumour causing 142
  argon laser trabeculoplasty, limitations, in 263
  blindness due to, Northern Transvaal 721
  blood groups as genetic markers in 270
  in ciliary body tumours 326
  filtering surgery, 5-fluorouracil liposomal delivery system for 688
  'low tension', primary empty sella and 852
  Molteno tube for, single stage insertion, modifications and 846
  neovascular, panretinal cryotherapy in 401
  oculokinetic and conventional perimetry compared in 258
  open angle: in birdshot chorioretinopathy 656
    chronic, photostress recovery in 641
    primary, early trabeculectomy compared with conventional management in 881
    treatment, adrenaline 1·0% and Propine 0·1% compared 465
  pathophysiology, photostress recovery time and 641
  risk factor in cataract 804
  uncontrolled, transscleral neodymium-YAG cyclocoagulation, in, short-term effects 615
Globe luxation:
  endophthalmitis and, in Crouzon's disease 196
  in histiocytosis X 631
Glomerulonephritis, mesangioproliferative, retinitis pigmentosa and 210
Graves' disease:
  neonatal 424
  ophthalmic, radiotherapy in 289
Graves' ophthalmopathy:
  correlation of clinical signs with measures derived from computed tomography 678
  effect of transantral orbital decompression on optic neuropathy in 683
  extraocular muscle volume, simple CT estimates and 674
Great Britain, retinoblastoma incidence, treatment and survival in, 1969–80 576
Guanethidine, consensual ophthalmotonic reaction and 750
Gwent, penetrating eye injuries, 10-year survey in 607

Haemangioma:
  cavernous, presenting as orbital mass after enucleation for chroidal melanoma 618
  ocular, complicated, radiotherapy in 287
Haemangiopericytoma, lacrimal sac 782
Haemoglobin:
  A_1, diabetics with cotton-wool spots and 666
  total, levels, in sickle cell retinopathy 727
Haemorrhage, retrobulbar, retrobulbar anaesthesia and 1
Head rest, surgical, new 284
Healonid, viscodelamination at vitreoretinal juncture in severe diabetic eye disease and 413
Hemianopia, homonymous, optic nerve hypoplasia and 180
Heredity/Hereditary:
  cataract, lamellar, central compaction in lens growth process and 538
  grouped pigmentation of retinal pigment epithelium 439
  uveal melanoma and 241
Herpes simplex, infection, vitamin A deficiency, measles and, corneal ulceration due to, Africa 879
Histiocytosis:
  sinus, massive lymphadenopathy and, eye in 793
  globe luxation in, cure 631
HLA A29, birdshot chorioretinopathy and 646
HLA typing, Yersinia-induced uveitis and, Ireland 939
Hodgkin's disease, malignant conjunctival lymphoma after 212
Horner's syndrome, consensual ophthalmotonic reaction and 750
Hyaluronidase, added to lignocaine with adrenaline for retrobulbar anaesthesia in senile cataract surgery 700
Hyperplasia, angiolymphoid, eosinophilia and, lacrimal gland in 710
Hypertension, ocular, adrenaline 1·0% and Propine 0·1% compared in 465
Hyperthyroidism:
  maternal, neonatal Graves' disease and 424
  pattern visual evoked potentials in 534
Hypotony, post-operative, Molteno tube insertion for glaucoma and 846

Immune activation, systemic, abnormal, ocular inflammation and 83
Immunohistology, vitreous, intraocular lymphoma and, review 905
Immunological analysis:
  aqueous, in candida endophthalmitis clinical study 313
    rabbit 309
Immunology:
  Fuchs' heterochromic cyclitis, aetiology, and 921
  relapsing retinal vasculitis and 442
Immunopathology, pars planitis in family and 5
Immunosuppression, chemotherapeutic ganciclovir for CMV retinitis in 521
Implant, Molteno, functioning, tissue response to 29
Incontinentia pigmenti, pseudoglioma, development and, in infant 452
India:
  evaluation of non-mydriatic camera in diabetics in 841

  ocular survey in, rapid cataract grading method and 801
Indomethacin, retinopathy 434
Injury, ocular:
  penetrating: darts and 511, 608
    seat belts and 609
    10-year survey, Gwent 607
  retained airgun pellet, orbital, survey 97
Insulin, treatment, intensified, effect on retinal vessels in diabetics 666
Interleukin-2 receptors, uveitis and 83
Intoxication, quinine, ocular 23, 221
Intraocular lens implantation:
  effect on combined extracapsular extraction with trabeculectomy, comparative study 741
  standard power, refraction results after 231
  to correct cyclic esotropia in unilateral traumatic aphakia 305
Intraocular pressure:
  carteolol: topical, effect on, placebo compared with 27
    2% and timolol 0·5%, effects on, in healthy volunteers 101
  control levobunolol and timolol compared 892
    in primary open angle glaucoma, early trabeculectomy and 881
  nifedipine, effect on, in normal subjects 216
  raised. in disseminated intravascular coagulation 377
    D-timolol, 0·25% L-timolol and placebo, effects on 469
  reduction prostaglandin D_2 and, rabbit 461
    in uncontrolled glaucoma, transscleral neodymium-YAG cyclocoagulation and 615
  rise, spontaneous, retinal circulation during 754
  12-hour control, carteolol 2% twice daily and 890
Invermectin, single-dose therapy, *Onchocerca volvulus* infection with ocular involvement and 561
Ireland:
  solar retinopathy following religious rituals in 931
  Yersinia-induced uveitis in 938
Iris:
  angiography, in anterior uveal melanocytic tumours 326
  atrophy argon laser treatment of lipid keratopathy 900
    quinine and 25
  naevus, fluorescein angiography and 334, 335

Jamaica:
  childhood blindness in 65
  children, sickle cell retinopathy in, cohort study 727

Kenya:
  Crouzon's craniofacial dysostosis in 196
  postmeasles blindness in children in 880
Keratitis:
  gram-negative, association with contact lens wear 926
  herpetic, severe, prevalence of visual impairment in clinic population and 530
  microbial. chronic alcoholism and 155
    predisposing factors in, contact lens wear and 926
  mycotic, topical silver sulphadiazine for 192
  neuroparalytic, tarsorrhaphy for, in MURCS association 236
Keratoconus, incidence in spring catarrh 41
Keratomycosis, topical silver sulphadiazine in 192
Keratopathy:
  bullous, endothelial cell morphology in patients undergoing cataract surgery and 409
  crystalline, infectious, after penetrating keratoplasty 628
  lipid. argon laser treatment 900
    bilateral, idiopathic 338
Keratoplasty:
  keratoconus in spring catarrh and 42
  penetrating: epithelial cyst in anterior chamber after 36
    infectious crystalline keratopathy after 628
    required in severe herpetic keratitis 530
Keratotomy, radial, corneal endothelial permeability evaluation and 274
Keratotorus, floppy eyelid syndrome and 634
Kidney failure, risk factor for cataract 806
Kimura's disease 712

Lacrimal:
  gland, angiolymphoid hyperplasia with eosinophilia involving 710
  sac, haemangiopericytoma 782
Landers lens, 'poor man's', 796
Laser:
  argon: photocoagulation, in central serous retinopathy, long-term follow-up of prospective trial of 829
    long-duration low-energy, of raised new vessels 837
    trabeculoplasty, therapeutic limitations 263
    treatment of lipid keratopathy 900
  photocoagulation, anterior segment ischaemia after, in systemic lupus erythematosus 11
Lead, levels, serum, retained airgun pellets and 97
Lens (crystalline):
  capsule, anterior, chemical debridement by EDTA and trypsin 406
  endothelium cell morphology examination, technique 409
      in patients undergoing cataract surgery 409
    morphometric study, corneas stored in MK media and warmed at 37°C and 545
  growth, process, central compaction in, lamellar cataract indicating 538
  posterior capsule thickening, after extracapsular extraction 483
  thickness: in early cataract 348
    measurement with slit-lamp microscope 344
Lens implant, *see* Intraocular lens
Lens (optical), Landers, 'poor man's', clinical application 796
Lensectomy, pars plicata, vitrectomy and, in congenital cataract 601
Lenticules, for epikeratophakia, lathing at room temperature, rabbit 354
Leucokoria, neurofibromatosis and retinoblastoma and 139
Levobunolol, in glaucoma, timolol compared with, 4-year study 892
Lichen sclerosus et atrophicus, morphoea and, acquired Brown's syndrome in 552
Lid/Lids:
  border, entropion in trichiasis 17
  canthus, medial, basal cell carcinoma, radiotherapy and, recurrence rates and 134
  congenital divided naevus 198
  contralateral choroidal melanoma metastasising to 456
  fatal necrotising fasciitis of 428
  floppy, syndrome, keratotorus and 634
  flora, bacterial, normal, preoperative fusidic acid and 206
  oedema, in disseminated intravascular coagulation 377

 reconstruction and repair, after atrophic blepharochalasis 863
 red swollen, testicular cancer presenting as 868
 retraction in Graves' ophthalmopathy, extraocular muscle enlargement in 674
 upper: lesions, spontaneous repair 856
  reformation, spontaneous 856
  sulcus, degree, cosmetic failure following excision of eye and 768
Lignocaine, hyaluronidase added to, with adrenaline, for retrobulbar anaesthesia in senile cataract surgery 700
Liposarcoma, primary myxoid, orbital 912
L-timolol, 0·25%, effect on raised intraocular pressure 469
L-tryptophan, antidote to ocular toxicity of PNU 584
Lupus erythematosus, systemic, anterior segment ischaemia following laser photocoagulation in 11
Lymphadenopathy, massive, sinus histiocytosis and, ocular involvement in 793
Lymphoma:
 intraocular: differentiation from uveitis 905
  immunological and cytological analysis 905
 malignant, bilateral ocular disease as initial presentation of 248

Macula/Macular:
 detachment, lymphomatous choroidal mass causing 251
 disease, photostress and 644
 hole, lamellar, idiopathic juxtafoveolar telangiectasia and 550
 obstructed capillary reflow, in diabetic retinopathy, fluorescein angiography and 660
 pucker, idiopathic, epiretinal membranes causing, vitrectomy for 692
Magnetic resonance scanning:
 neonatal Graves' disease and 424
 in Tolosa-Hunt syndrome 299
Marcus Gunn phenomenon, levator palpebrae superioris histology in 104
Measles, blindness after 879
Medulloepithelioma, diagnosis and treatment 764
Meibomian cyst, management by general practitioners in community 733
Meibomian glands, orifices, lid border trichiasis and 21
Melanoma:
 choroidal: enucleation for, cavernous haemangioma presenting as orbital mass after 618
  justification of radiation treatment in 317, 319
  malignant: bilateral primary 244
   in naevus of Ota 131
  radiotherapy and 558, 559
 intraocular, S-100 protein detection and quantification in ocular tissues and fluids in 874
 ocular, intracerebral metastases from 246
 uveal: familial 241
  treatment, cobalt plaque versus enucleation, survival rates compared 495
Meningitis, cryptococcal, presenting as uveitis 167
Methanol, poisoning, optic nerve involvement in 778
Methylcellulose, viscodelamination at vitreoretinal juncture in severe diabetic eye disease and 413
Metoclopramide, ocular hypotensive action of timolol and 598
Microdensitometer, computerised scanning, retinal vessel photographs, insulin treatment in diabetics and 666
Microscope/Microscopy:
 electron, *see* Electron microscopy
 slit-lamp, depth measurement with 344
 specular, eye bank corneas 545
MIG welder, retinal burns caused by 570
Military base, employment on, risk factor for cataract 804
Mohs' surgery, in periocular basal cell carcinoma 134
Molteno implant, functioning, tissue response to aqueous drainage in 29
Molteno tube, single stage insertion, modifications and 846
Morphoea, combined lichen sclerosus et atrophicus and, acquired Brown's syndrome in 552
Morphometry:
 automated, corneal endothelial cells 68
 levator palpebrae superioris in Marcus Gunn phenomenon 104
Movements, extraocular, restriction, in disseminated intravascular coagulation 377
Movements, ocular, vergence, disordered control, in dyslexia 162
Multiple sclerosis, one-and-a-half syndrome correlated with pontine lesion in, nuclear magnetic resonance imaging and 515
MURCS association, congenital corneal anaesthesia and 236
Muscles:
 extraocular: rectus, bilateral, pseudoparalysis, early onset convergent strabismus and 110
   bimedial recession, early-onset strabismus and 110
  simplified measurement, CT and, in Graves' ophthalmopathy, optic neuropathy development and 674
  volume, CT estimates, in Graves' ophthalmopathy 674
 levator palpebrae superioris, histology in Marcus Gunn phenomenon 104
Myopexy, retroequatorial: 111
 bimedial rectus recession and, strabismus and 110
Myopia, corneal shape and astigmatism and 696

Naevus:
 congenital, divided, of lids 198
 of Ota, malignant choroidal melanoma in 131
Nasolacrimal duct, ultrasound examination, adrenaline dacryolith detection by 935
Neurofibromatosis:
 pedigree 140
 retinoblastoma and 139
Nifedipine:
 effect on intraocular pressure in normal subjects 216
 risk factor for cataract 809
Nigeria, postmeasles blindness in children in 880
Nocardiosis:
 endophthalmitis and 55
 nosological and microbiological aspects, review 55
Norrie's disease, in Asian family 62
Northern Transvaal, blindness, prevalence and causes, in 721
N-3-pyridylmethyl-N'-*p*-nitrophenylurea, ocular toxicity in man and rabbit 584
Nuclear magnetic resonance:
 axial scan, orbital liposarcoma 915
 imaging, pontine lesion demonstrated by, in multiple sclerosis, one-and-a-half syndrome and 515
Nystagmus, optic nerve hypoplasia and 179, 180

Obituary:
 GURD, SURGEON REAR-ADMIRAL DUDLEY PLUNKETT 400
 HARCOURT, RICHARD BRIAN 320

MACFETRIDGE, HERBERT FITZROY TOWNSEND 160
Ocular tension, *see* Intraocular pressure
Onchocerca volvulus**,** infection, with ocular involvement, single-dose invermecting therapy in 561
Onchocerciasis, ocular, single-dose invermectin therapy and 561
One-and-a-half syndrome, nuclear magnetic resonance imaging of pontine lesion in multiple sclerosis and 515
Ophthalmia:
  chlamydial, adult, marginal corneal abscess and 774
  neonatorum, gonococcal, treatment, intramuscular cefotaxime 518
Ophthalmic artery, perfusion pressure, changes, postural 253
Ophthalmic Literature, revised and improved 480
Ophthalmic surgery:
  corneal clouding and 399
  failure after gas injection 321, 322
  head rest 284
  instruments. Ciapryna coaxial cannula 485
    modified irrigating-aspirating needle 368
  micro-, closed, for severe diabetic eye disease, viscodelamination at vitreoretinal juncture in 413
Ophthalmic survey, of diabetic clinic 160
Ophthalmomyiasis, interna posterior, reindeer warble fly larvae causing, acute vitrectomy in 420
Ophthalmoscopy, indirect, retinal surface light reflex alterations during, retinal elevation assessment and 703
Ophthalmotonic reaction, consensual 746
    sympathetic influences on 750
Optic:
  disc· changes, classification at diagnosis of primary open angle glaucoma 882
    new vessels, origin, videofluorographic assessment 394
  nerve: development, hypoplasia, mechanisms, and 176
    head, in birdshot chorioretinopathy 646
    hypoplasia, localising patterns of 176
    involvement in Graves' ophthalmopathy, mid-orbital slice of CT scan and 678
    necrosis, central, fatal methanol poisoning and 778
  neuropathy. development, extraocular muscles and, in Graves' ophthalmopathy 674, 678
    in Graves' ophthalmopathy, effect of transantral orbital decompression on 683
Ora serrata, retinal magnification factor calculation at 228
Orbit/Orbital:
  choroidal melanoma metastasising to 456
  decompression, transantral, effect on optic neuropathy in Graves' ophthalmopathy 683
  disease, benign, radiotherapy in 286, 289
  Ewing's sarcoma, primary, visual loss and 786
  haemangioma, cavernous, bilateral 871
  histiocytosis X, radiotherapy in 289
  injury, penetrating, posterior, retained foreign body and 432
  liposarcoma, primary myxoid 912
  mass, cavernous haemangioma presenting as, after enucleation for choroidal melanoma 618
  pseudotumour, precipitating acute angle closure glaucoma 142
  retained airgun pellets in, management 97
  vasculitis, visual recovery in 737
  volume, loss, quantification, after excision 768
Orbitography:
  radio-opaque dye penetrating subdural space and 78
Oslo Study 667
Osteoma, choroidal, in pregnancy 612
Oxfordshire, case-control study of cataract in, risk factors and 804
Oxygen, treatment, increased procollagenase activating angiogenic factor in vitreous and, kitten 2

Panophthalmitis, *Clostridium septicum* 380
Parotid gland, angiolymphoid hyperplasia with eosinophilia and 710
Pars planitis:
  chronic inflammation in, helper T cells and 5
  familial, clinical and immunopathological studies 5
  snowbanking and, in brothers 5
Perimetry, oculokinetic and conventional compared, in glaucoma 258
PERK (prospective evaluation of radial keratotomy), study patients, corneal endothelial permeability evaluation in 274
Pharmacokinetics, 5-fluorouracil liposomal delivery system 688
Photocoagulation:
  laser. anterior segment ischaemia after, systemic lupus erythematosus and 11
    argon laser, in central serous retinopathy, long-term follow-up of prospective trial of 829
  of raised new vessels, long-duration low-energy argon laser 837
Photography:
  retinal vessels, intensified insulin treatment in diabetics and 666
  slit-lamp, spot metering system and 473
  specular, endothelial cells of human corneas stored in MK media 545
Photostress recovery:
  in chronic open angle glaucoma 641
  time, pharmacological meiosis and 641
Pigeons, cryptococcosis and 169, 171
Plombage, suprachoroidal, urethane based hydrophilic polymer and, rabbit 278
PNU rat poison:
  gentamicin preventing ocular toxicity due to 584
  ocular toxicity in man and rabbit 584
Polyarteritis nodosa, chronic renal failure and, orbital vasculitis with sudden visual loss in 737
Polymer, hydrophilic, urethane based, suprachoroidal plombage with, rabbit 278
Posture, perfusion pressure and retinal arteriolar calibre changes and 253
Pregnancy, choroidal osteoma in 612
Procollagenase activating angiogenic factor, increase in vitreous, oxygen treatment and, kitten 2
Propine 0·1%, adrenaline 1·0% compared with, in open-angle glaucoma and ocular hypertension 465
Proptosis:
  disseminated intravascular coagulation and 377
  orbital myxoid liposarcoma and 915
  unilateral, clinical presentation in primary angiosarcoma of skull 713
Prostaglandin D_2, intraocular pressure reduction and, rabbit 461
Pseudoglioma, development, infant with incontinentia pigmenti 452
Ptosis, periorbital swelling and, malignant lymphoma presenting as 249
Pupil/Pupillary:
  defect, optic nerve hypoplasia and 179
  dilatation, blindness due to quinine toxicity and 222
  vermiform motion, quinine overdose and 23

- **Quinine toxicity:**
  - blindness due to 219
  - ocular 23

- **Radioimmunoassay**, S-100 protein detection and quantification in ocular tissues and fluids in intraocular melanoma and 874
- **Radiotherapy:**
  - in benign orbital disease 286, 289
  - choroidal melanoma and: 558, 559
    - justification 317, 319
  - in complicated ocular angiomas 287
  - in ophthalmic Graves' disease 289
  - in orbital histiocytosis X 289
  - periocular basal cell carcinoma, recurrence rate and 134
- **Refraction:**
  - error. acute change, lymphomatous deposit in choroid causing 249
    - simulated, stereoscopic evoked responses to crossed and uncrossed disparity accompanying 759
  - evolution in early-onset strabismus 110
  - stabilisation after cataract surgery 815
  - results, anterior chamber lens implantation and 231
- **Reindeer warble fly**, larvae, intraocular infestation, acute vitrectomy in 420
- **Religious rituals**, solar retinopathy following 931
- **Retina/Retinal:**
  - arterial disease, systemic lupus erythematosus and, ischaemia following photocoagulation in 11
  - arteriolar calibre, postural changes 253
  - artery, central, thrombosis, clostridial bacteraemia and 380
  - branch arteriolar occlusion, with chicken-pox 78
  - burns, exposure to MIG-welding arcs causing 570
  - circulation: during spontaneous intraocular pressure rise 754
    - transient ischaemic lesions in diabetics on intensified insulin treatment and 666
  - cotton-wool spots, insulin infusion, continuous subcutaneous, effect on retinal vessels in diabetics, and 666
  - detachment: aphakic, surgery, prospective study 820
    - in birdshot chorioretinopathy 656
    - surgery. failure after gas injection 321, 322
      - suprachoroidal plombage with urethane based hydrophilic polymer, rabbit 278
  - elevation: assessment, novel clinical technique for 703
    - clinical assessment, review 703
  - exudation, posterior uveitis in cryptococcal meningitis and 167
  - haemodynamic changes, spontaneous intraocular pressure rise and 754
  - inflammatory lesion, fatal disseminated cryptococcosis and 171
  - magnification factor, calculation at ora serrata, method 228
  - neovascularisation, systemic lupus erythematosus and, ischaemia following photocoagulation in 11
  - non-perfused area, enlargement with progression of diabetic retinopathy 660
  - oedema, chicken-pox and 79
  - pigment epitheliopathy, acute posterior multifocal placoid, sarcoidosis and 74
  - pigment epithelium. detachment, photocoagulation for, bilateral pigment epithelium tears after 621
    - familial grouped pigmentation 439
    - tears: bilateral 621
      - bilaterality 918
  - proteins, uveogenic 81
  - quinine toxicity, treatment 24
  - S-antigen, inoculation to rats, posterior uveitis induced by 88
  - specific autoantibodies, in relapsing retinal vasculitis 443
  - surface light reflexes, during indirect ophthalmoscopy, retinal elevation assessment and 703
  - vasculitis, relapsing, longitudinal study of clinical and immunological findings in 442
  - vasculopathy, in birdshot chorioretinopathy 646
  - vessels: in diabetics, intensified insulin treatment, effects on 666
    - light reflex, diabetes and 671
    - peripheral, closure, Jamaican children with sickle cell disease and 727
- **Retinitis:**
  - cytomegalovirus. in AIDS, Ganciclovir treatment in, active cytomegalovirus particles in eyes and 293
    - AZT treatment in AIDS aggravating 239
    - ganciclovir treatment 525
      - in AIDS or chemotherapeutic immunosuppression 521
- **Retinitis pigmentosa**, mesangioproliferative glomerulonephritis and 210
- **Retinoblastoma:**
  - in Great Britain, 1969–80, incidence, treatment and survival 576
  - neurofibromatosis and 139
- **Retinopathy:**
  - central serous, argon laser photocoagulation in, long-term follow-up of prospective trial of 829
  - diabetic. evaluation of non-mydriatic camera for, in India and Europe 841
    - obstructed macular capillary reflow in, fluorescein angiography and 660
    - ophthalmic survey of diabetic clinic and 160
    - panretinal cryotherapy in 401
    - proliferative, complicated, surgery, viscodelamination and 413
    - worsening with intensified insulin treatment 666
  - indomethacin 434
  - of prematurity, pathogenesis, experimental studies, kitten 363
  - sickle cell: haemoglobin and fetal haemoglobin levels and 727
    - in Jamaican children, cohort study 727
  - solar, after religious rituals 931
- **Road traffic accidents**, penetrating ocular injuries and, statistics 607
- **Rubella syndrome**, congenital blindness in Jamaica and 65
- **Rubeosis:**
  - medulloepithelioma, diagnosis, and 764
  - panretinal cryotherapy for 401

- **Sarcoidosis**, acute posterior multifocal placoid pigment epitheliopathy and 74
- **Sarcoma**, Ewing's, primary, orbital, visual loss and 786
- **Seat belts**, penetrating ocular injuries and 609
- **Sella**, empty, primary, 'low tension glaucoma', and 852
- **Serum albumin**, level in tear fluids in acute adenovirus conjunctivitis 390
- **Sickle cell disease**, early ocular changes in 727
- **Silver sulphadiazine**, topical, in ocular keratomycosis 192
- **Sinusitis**, allergic aspergillus, visual failure in 127
- **Skull**, primary angiosarcoma, presenting as unilateral proptosis 713
- **Slit-lamp:**
  - microscope, depth measurement with 344

photography, spot metering system and . . 473
Snowbank, pars planitis and, clinical and immunopathological studies in 5
Spironolactone, risk factor for cataract 809
Sport, penetrating ocular injuries and, statistics . . 607
Squint, *see* Strabismus
Sri Lanka, Norrie's disease in 62
Staphylococcus aureus, endophthalmitis, metastatic . 189
Staphylococcus epidermidis, endophthalmitis, vitrectomy in 386
Steroids, risk factor for cataract 809
Stevens-Johnson syndrome, metaplastic eyelashes and 21
Strabismus:
  early-onset, surgery, postponement 110
    results 113
  optic nerve hypoplasia and 177
  parallel 161
  surgery, early 110
Streptococcus pyogenes, necrotising fasciitis due to . . . 430
Sturge-Weber syndrome, variant, treatment, radiotherapy 287
Subretinal membrane, changing fluorescein angiographic appearance 835
Sympathetic influences on consensual ophthalmotonic reaction 750
Synoptophore, vergence eye movements in dyslexic children and 162
S-100 protein, detection and quantification in ocular tissues and fluids from intraocular melanoma patients 874

Tachycardia, topical carteolol 2% and timolol 0·5% and, in healthy volunteers 101
Tanzania, postmeasles blindness in 879, 880
Tape recorder, video, automated corneal endothelial cell morphometry and 68
T cells:
  activated, in uveitis 83
  activation, stages in uveitis, colour flow cytometry techniques and 83
  uveitis and 82
Tear fluids, α_1-antitrypsin and serum albumin levels in, in acute adenovirus conjunctivitis 390
Telangiectasia, juxtafoveolar, idiopathic, lamellar macular hole and 550
Testicles, cancer, presenting as red swollen lid 868
Thalassaemia, beta, minor, angioid streaks in . . 303
Timolol:
  compared with levobunolol in glaucoma, 4-year study 892
  consensual ophthalmotonic reaction and . . . 750
  ocular hypotensive action, dopamine-2 receptor blockade and 598
  0·5%, ocular and cardiovascular response to, in healthy volunteers 101
  12-hours intraocular pressure control by, carteolol compared 890
Tissue culture, primary, growth and contractility of cells from fibrocellular epiretinal membranes in . 116
Tissues, ocular:
  intravitreal fibroblast injection and (rabbit) . . . 498
  response to functioning Molteno implant, microscopic study 29
T lymphocytes, *see* T cells
Tobacco, risk factor for cataract 807, 810
Tolosa-Hunt syndrome, computerised axial tomography and magnetic resonance scanning in . . . 299
Tomography, computer-aided:
  axial acute angle closure glaucoma due to orbital pseudotumour and 142
    primary myxoid orbital liposarcoma 912
  cavernous haemangioma presenting as orbital mass after enucleation for choroidal melanoma . . 618
  choroidal osteoma, in pregnant woman . . . 612
  correlation of clinical signs of Graves' ophthalmopathy with measures derived from 678
  intracerebral metastases from ocular melanoma . 247
  lacrimal gland involvement in angiolymphoid hyperplasia and 710
  magnetic resonance imaging scan, bilateral orbital cavernous haemangioma and . . . 871
  metrizamide, primary empty sella and 'low tension glaucoma' and 854
  mid-orbital slice, measurements on, Graves' ophthalmopathy, diagnosis and . . . 678
  neonatal Graves' disease and 424
  ophthalmic complications in disseminated intravascular coagulation and 377
  ophthalmic Graves' disease and 291
  optic nerve hypoplasia and . . . 179, 180
  orbit, primary Ewing's sarcoma and 788
  orbital histiocytosis X and 291, 292
  orbital liposarcoma, myxoid, and 914
  orbital lymphoma infiltration and 249
  retained foreign body after posterior penetrating orbital injury 433
  simple estimates of extraocular muscle volume in Graves' ophthalmopathy and 674
  skull, primary angiosarcoma, and 714
  in Tolosa-Hunt syndrome 299
Toxicity, ocular:
  air gun pellets and 99
  quinine causing 23
Trabeculectomy:
  early, in primary open angle glaucoma, conventional management compared 881
  extracapsular extraction combined with, effect of intraocular lens implantation on, comparative study 741
Trabeculoplasty, argon laser, therapeutic limitations 263
Trachoma, blindness and, Northern Transvaal . . 721
Trichiasis:
  causes 20
  presumed, morphological observations in . . . 17
Trypsin, EDTA and, lens epithelial cell debridement by 406
Tumour, melanocytic, anterior uvea, fluorescein angiography in 326

Ultrasound/Ultrasonography:
  examination, nasolacrimal duct, adrenaline dacryolith detection by 935
  orbital, contralateral metastasis from choroidal melanoma and 456
Uvea/Uveal:
  anterior, melanocytic tumours, fluorescein angiography 326
  melanoma: familial 241
    spindle cell, angiography 336
    treatment, cobalt plaque versus enucleation, survival rates compared 495
Uveitis:
  activated T lymphocytes in 83
  acute anterior: 81
    α_1-antitrypsin phenotypes in 636
  cryptococcal meningitis presenting as . . . 167
  idiopathic, peripheral T lymphocyte activation and 83

posterior: experimental, ERG studies in 88
retinal S antigen and 81
progress in 81
Yersinia-induced, in Ireland 938

Vascularisation, intravitreal, induction, mechanism 2
VDU, *see* Visual display unit
VER, *see* Visually evoked responses
Vergence, control, disordered, in dyslexic children 161, 162
Videofluorography, origin of disc new vessels assessed by 394
Vision:
impairment in severe herpetic keratitis 530
loss: acute, quinine toxicity and 23
primary Ewing's sarcoma of orbit with 786
rapid progressive, in allergic aspergillus sinusitis 127
sudden, clostridial bacteraemia and 380
Visual acuity, *see* Acuity, visual
Visual display unit, high-resolution, visual after-effects associated with using 823
Visual fields, *see* Fields, visual
Visual pathways:
developing, optic nerve hypoplasia due to damage at any site in 176
development 176
Visual problems, in dyslexia, causes 162
Visual evoked potentials, pattern, in hyperthyroidism 534
Visually evoked responses:
blindness due to quinine toxicity and 221
stereoscopic, to crossed and uncrossed disparity accompanying simulated refractive error 759

Vitamin A deficiency, measles and herpes simplex infection, corneal ulceration due to, Africa 879
Vitrectomy:
acute, in intraocular infestation by reindeer warble fly larvae 420
idiopathic epiretinal membranes causing macular pucker and 692
'poor man's' Landers lens and 796
role in *Staphylococcus epidermidis* endophthalmitis 386
Vitreoretinal juncture, viscodelamination at, in severe diabetic eye disease 413
Vitreous:
gas injection, surgical failure after 321, 322
increased procollagenase activating angiogenic factor in, oxygen treatment and, kitten 2
S-100 protein detection in, intraocular melanoma and 874
specimens, cytology and immunohistology, intraocular lymphoma and 905
Vitritis, radiation from optic disc and, in birdshot chorioretinopathy 646

Welding, MIG-, retinal burns caused by 570

X-rays:
Hodgkin's disease 213
primary Ewing's sarcoma of orbit and 786

Yersinia, uveitis due to, Ireland 938
Yugoslavia, solar retinopathy following religious rituals in 931

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Contents

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Editorial: Why retrobulbar anaesthesia? REDMOND J H SMITH ... 1
Increased procollagenase activating angiogenic factor in the vitreous humour of oxygen treated kittens C M TAYLOR, J B WEISS, B McLAUGHLIN, R D KISSUN, AND A GARNER ... 2
Clinical and immunopathological studies of pars planitis in a family RICHARD P WETZIG, CHI-CHAO CHAN, ROBERT B NUSSENBLATT, ALAN G PALESTINE, DAVID O MAZUR, AND KAMAL K MITTAL ... 5
Anterior segment ischaemia following laser photocoagulation in a patient with systemic lupus erythematosus BRADLEY F JOST, R JOSEPH OLK, ARNALL PATZ, STUART L FINE, AND ROBERT P MURPHY ... 11
Morphological observations on patients with presumed trichiasis K BARBER AND T DABBS ... 17
Ocular quinine toxicity CHRIS R CANNING AND SUSAN HAGUE ... 23
A double-crossover trial comparing the effects of topical carteolol and placebo on intraocular pressure G R DUFF AND P A GRAHAM ... 27
Tissue response to aqueous drainage in a functioning Molteno implant K U LOEFFLER AND J L JAY ... 29
Epithelial cyst in the anterior chamber after penetrating keratoplasty: a rare complication CHARLES CLAOUÉ, STASIA LEWKOWICZ-MOSS, AND DAVID EASTY ... 36
Incidence of keratoconus in spring catarrh M DAUD KHAN, NIAMATULLAH KUNDI, NASIR SAEED, ARIFA GULAB, AND ANISA F NAZEER ... 41
Contrast sensitivity and acuity relationship in strabismic and anisometropic amblyopia M ABRAHAMSSON AND J SJOSTRAND ... 44
Grating and recognition acuities of young amblyopes M J MOSELEY, A R FIELDER, J R THOMPSON, C MINSHULL, AND D PRICE ... 50
Nocardial endophthalmitis: report of two cases studied histopathologically ANDREW P FERRY, RAMON L FONT, ROBERT S WEINBERG, MILTON BONIUK, AND CHARLES L SCHAFFER ... 55
Norrie's disease in an Asian family D G HARENDRA DE SILVA AND D B K DE SILVA ... 62
Childhood blindness in Jamaica B J MORIARTY ... 65
Automated morphometry of corneal endothelial cell: use of video camera and video tape recorder OKIHIRO NISHI AND KOICHI HANASAKI ... 68
Acute posterior multifocal placoid pigment epitheliopathy and sarcoidosis D J DICK, P K NEWMAN, J RICHARDSON, R WILKINSON, AND A R MORLEY ... 74
Correspondence ... 78
Note ... 80

No. 2 February 1988

Editorial: Progress in uveitis D J SPALTON ... 81
Activated T lymphocytes in uveitis JEAN DESCHÊNES, DEVRON H CHAR, AND SHAWNYA KALETA ... 83
Experimental posterior uveitis. II. Electroretinographic studies M R STANFORD AND J ROBBINS ... 88
On the management of retained airgun pellets: a survey of 11 orbital cases NICHOLAS A JACOBS AND LAURENCE H MORGAN ... 97
Ocular and cardiovascular response to topical carteolol 2% and timolol 0·5% in healthy volunteers D J BRAZIER AND S E SMITH ... 101
Histological appearances of the levator palpebrae superioris muscle in the Marcus Gunn phenomenon R W LYNESS, J R O COLLIN, R A ALEXANDER, AND A GARNER ... 104
Why should surgery for early-onset strabismus be postponed? M DELLER ... 110
Growth and contractility of cells from fibrocellular epiretinal membranes in primary tissue culture D Y JIANG, P S HISCOTT, I GRIERSON, AND D MLEOD ... 116
Visual failure in allergic aspergillus sinusitis IAIN S DUNLOP AND FRANK A BILLSON ... 127
Malignant melanoma of the choroid in a naevus of Ota MOHINDER SINGH, BALJIT KAUR, AND NORIZAN MOHD ANNUAR ... 131
Radiotherapy of periocular basal cell carcinomas: recurrence rates and treatment with special attention to the medical canthus RENE S RODRIGUEZ-SAINS, PERRY ROBINS, BYRON SMITH, AND STEPHEN L BOSNIAK ... 134
Neurofibromatosis associated with retinoblastoma BERATI HASANREISOĞLU, MERAL OR, AND HALUK AKBATUR ... 139

Acute angle closure glaucoma precipitated by orbital pseudotumour LILLY ZBOROWSKI-GUTMAN, ISAAC GUTMAN, VARDA CHEN, MORDECHAI SHARIR, AND GIDEON FINDLER 142
Changes in astigmatism between the ages of 1 and 4 years: a longitudinal study M ABRAHAMSSON, G FABIAN, AND J SJOSTRAND 145
Drug delivery through soft contact lenses M R JAIN 150
Chronic alcoholism and microbial keratitis L DAVID ORMEROD, DEBORAH S GOMEZ, DAVID J SCHANZLIN, AND RONALD E SMITH 155
Correspondence 160
Obituary 160
Note 160

No. 3 March 1988

Editorial: The parallel squint REDMOND J H SMITH 161
Disordered vergence control in dyslexic children J F STEIN, P M RIDDELL, AND S FOWLER 162
Cryptococcal meningitis presenting as uveitis S P STONE, J BENDIG, J HAKIM, P E KINNEAR, B S AZADIAN, AND F CLIFFORD-ROSE 167
Fatal disseminated cryptococcosis following intraocular involvement JOEL A SCHULMAN, CHRISTOPHER LEVEQUE, MARION COATS, LINDA LAWRENCE, AND JOHN C BARBER 171
Localising patterns of optic nerve hypoplasia—retina to occipital lobe P NOVAKOVIC, D S I TAYLOR, AND W F HOYT 176
Corneal elastosis within lattice dystrophy lesions JACOB PE'ER, BEN S FINE, ANITA DIXON, AND DAVID S ROTHBERG 183
Metastatic *Staphylococcus aureus* endophthalmitis: a case report C J O'BRIEN AND G M KYLE 189
Topical silver sulphadiazine—a new drug for ocular keratomycosis MADAN MOHAN, S K GUPTA, V K KALRA, R B VAJPAYEE, AND MAHIPAL S SACHDEV 192
Crouzon's craniofacial dysostosis in Kenya HARJINDER S CHANA AND VOLKER KLAUSS 196
Congenital divided naevus of the eyelids P J McDONNELL AND B J MAYOU 198
Extratarsal chalazia RUSSELL S GONNERING 202
Effect of preoperative fusidic acid on the normal eyelid and conjunctival bacterial flora PETER B TAYLOR, KHALID F TABBARA, AND EILEEN M BURD 206
Mesangioproliferative glomerulonephritis associated with retinitis pigmentosa P A KALRA AND J H TURNEY 210
Malignant lymphoma of the conjunctiva following Hodgkin's disease HANS E GROSSNIKLAUS, DIANE C FARHI, BRUCE R JACOBSON, AND MARY FAITH ABBUHL 212
Effect of the calcium antagonist nifedipine on intraocular pressure in normal subjects S P KELLY AND T J WALLEY 216
Blindness from quinine toxicity P BACON, D J SPALTON, AND S E SMITH 219
Effectiveness of a decontamination method for donor corneas P R BADENOCH, S J ALFRICH, T R WEDDING, AND D J COSTER 225
Image size in the fundus: structural evidence for wide-field retinal magnification factor A L HOLDEN AND F W FITZKE 228
Pre- and postoperative refraction after cataract extraction with implantation of standard power IOL THOMAS OLSEN 231
Congenital corneal anaesthesia and the MURCS association: a case report L ESAKOWITZ AND J R W YATES 236
Correspondence 239
Notes 240
Correction 240

No. 4 April 1988

Familial uveal melanoma C R CANNING AND J HUNGERFORD 241
Two cases of primary bilateral malignant melanoma of the choroid STEFAN SEREGARD, CARL DAUNIUS, ERIK KOCK, AND VLADISLAV POPOVIC 244
Intracerebral metastases from ocular melanoma D RUSSEL JONES, I N SCOBIE, AND N J C SARKIES . . 246
Bilateral ocular disease as the initial presentation of malignant lymphoma ROBERT WEISENTHAL, WILLIAM C FRAYER, CHARLES W NICHOLS, AND RALPH C EAGLE 248

Postural changes in perfusion pressure and retinal arteriolar calibre S HAGUE AND D W HILL 253
Comparative evaluation of oculokinetic perimetry and conventional perimetry in glaucoma EMILIO ALVAREZ, BERTIL E DAMATO, JEFFREY L JAY, AND ELIZABETH McCLURE 258
Therapeutic limitations of argon laser trabeculoplasty AUSTIN I FINK, ALAN J JORDAN, PAUL N LAO, AND DOROTHY A PONG 263
Blood groups as genetic markers in glaucoma ANNE M V BROOKS AND W E GILLIES 270
The evaluation of corneal endothelial permeability in PERK study patients JANET B SERLE, PENNY A ASBELL, STEPHEN A OBSTBAUM, STEVEN M PODOS, AND NGOC ANH-LE 274
Experimental suprachoroidal plombage with a urethane based hydrophilic polymer W S FOULDS, DOROTHY AITKEN, AND W R LEE 278
A new surgical head rest B L HALLIDAY 284
Radiotherapy in benign orbital disease. I: Complicated ocular angiomas P N PLOWMAN AND A N HARNETT 286
Radiotherapy in benign orbital disease. II· Ophthalmic Graves' disease and orbital histiocytosis X A N HARNETT, D DOUGHTY, A HIRST, AND P N PLOWMAN 289
Active cytomegalovirus particles in the eyes of an AIDS patient being treated with 9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine (Ganciclovir) STEVEN A TEICH, JAY CASTLE, ALAN H FRIEDMAN, WILLIAM SIROTY, JUAN ORELLANA, AND MILDRED SCHMITTERER 293
Computerised axial tomography and magnetic resonance scanning in the Tolosa-Hunt syndrome D J B THOMAS, M C CHARLESWORTH, F AFSHAR, AND D J GALTON 299
Angioid streaks in beta thalassaemia minor FRANK P KINSELLA AND DAVID J MOONEY 303
Cyclic esotropia in a patient with unilateral traumatic aphakia: case report M D COLE, A HAY, AND E M EAGLING 305
Immunological analysis of the aqueous humour in candida endophthalmitis. I: Experimental study F MALECAZE, M H BESSIERES, P BEC, S FLEUTIAUX, A MATHIS, AND J P SEGUELA 309
Immunological analysis of the aqueous humour in candida endophthalmitis. II. Clinical study A MATHIS, F MALECAZE, M H BESSIERES, J L ARNE, J P SEGUELA, AND P BEC 313
Correspondence 317
Obituary 320
Note 320

No. 5 May 1988

Editorial: Surgical failure after gas injection REDMOND J H SMITH 321
Failed retinal surgery caused by intraocular gas injection P B JOHNSTON, C J F MAGUIRE, AND W C LOGAN 322
Fluorescein angiography of anterior uveal melanocytic tumours J K DART, R J MARSH, A GARNER, AND R J COOLING 326
Idiopathic bilateral lipid keratopathy EDUARDO ALFONSO, LOURDES ARRELLANES, S ARTHUR BORUCHOFF, L DAVID ORMEROD, AND DANIEL M ALBERT 338
Depth measurement with the slit-lamp microscope E S PERKINS 344
Lens thickness in early cataract E S PERKINS 348
Experimental epikeratophakia using tissue lathed at room temperature CHAD K ROSTRON, JOHN H SANDFORD-SMITH, AND DAVID B MORTON 354
Treatment of senile entropion with botulinum toxin J R CLARKE AND D J SPALTON 361
Experimental studies on the pathogenesis of retinopathy of prematurity MAREK PROST 363
A modified irrigating-aspirating needle P T C DOCHERTY 368
K-Sol corneal preservation at room temperature KOICHI TAMAKI, EMILY D VARNELL, AND HERBERT E KAUFMAN 370
Ophthalmic complications with disseminated intravascular coagulation RICHARD B PATCHETT, W BRUCE WILSON, AND PHILIP P ELLIS 377
Sudden visual loss associated with clostridial bacteraemia ANTHONY J CANNISTRA, DANIEL M ALBERT, DONALD A FRAMBACH, ROBERT J DREHER, AND LLOYD ROBERTS 380
Role of vitrectomy in *Staphylococcus epidermidis* endophthalmitis LINDA A FICKER, TRAVIS A MEREDITH, LOUIS A WILSON, AND HENRY J KAPLAN 386
α_1-Antitrypsin and serum albumin in tear fluids in acute adenovirus conjunctivitis A K GUPTA, G S SARIN, M D MATHUR, AND B GHOSH 390
Origin of disc new vessels assessed by videofluorography N A JACOBS, C A STEELE, AND K B MILLS . 394
Correspondence 399
Obituary 400
Note 400

No. 6 June 1988

Panretinal cryotherapy in neovascular disease STEPHEN A VERNON AND HUNG CHENG 401
The Human Anterior Lens Capsule – an attempted chemical debridement of epithelial cells by ethylenediaminetetracetic acid (EDTA) and trypsin R C HUMPHRY, E G DAVIES, T J C JACOB, AND G M THOMPSON 406
Bullous keratopathy: a study of endothelial cell morphology in patients undergoing cataract surgery A K BATES AND H CHENG 409
Viscodelamination at the vitreoretinal juncture in severe diabetic eye disease DAVID MLEOD AND CHARLES R JAMES 413
Intraocular infestation by the reindeer warble fly larva: an unusual indication for acute vitrectomy M GJÖTTERBERG AND S O INGEMANSSON 420
Neonatal Graves' disease C LALLY SHIELDS, LEONARD B NELSON, GARY C CARPENTER, AND JERRY A SHIELDS 424
A fatal case of necrotising fasciitis of the eyelid R WALTERS 428
Posterior penetrating injury of the orbit with retained foreign body D G CHARTERIS 432
Indomethacin retinopathy: case report and review C M GRAHAM AND R K BLACH 434
Familial grouped pigmentation of the retinal pigment epithelium PAUL T V M DE JONG AND J WILLEM DELLEMAN 439
A longitudinal study of clinical and immunological findings in 52 patients with relapsing retinal vasculitis M R STANFORD, ELIZABETH GRAHAM, EVA KASP, M D SANDERS, AND D C DUMONDE 442
Conjunctival anaerobic and aerobic bacterial flora in paediatric versus adult subjects THOMAS R SINGER, SHERWIN J ISENBERG, AND LEONARD APT 448
Incontinentia pigmenti: the development of pseudoglioma C A BROWN 452
Metastasis of choroidal melanoma to the contralateral choroid, orbit, and eyelid JERRY A SHIELDS, CAROL L SHIELDS, ERIC P SHAKIN, AND LARRY E KOBETZ 456
Prostaglandin D_2 reduces intraocular pressure YASUMASA GOH, MASAYUKI NAKAJIMA, IKUO AZUMA, AND OSAMU HAYAISHI 461
A single-blind randomised trial comparing adrenaline 1·0% with dipivalyl epinephrine (Propine) 0·1% in the treatment of open-angle glaucoma and ocular hypertension K B MILLS AND N A JACOBS 465
A study of the effects of four concentrations of D-timolol, 0·25% L-timolol, and placebo on intraocular pressure on patients with raised intraocular pressure K B MILLS, N J JACOBS, AND R VOGEL 469
Slit-lamp photography made easy by a spot metering system P T KHAW AND A R ELKINGTON 473
Book reviews 475
Notes 480

No. 7 July 1988

Changing patterns of early complications in cataract surgery with new techniques: a surgical audit J F ACHESON, J D McHUGH, AND M G FALCON 481
The Ciapryna coaxial cannula R V PEARSON AND J D JAGGER 485
Control of astigmatism in cataract surgery NICHOLAS A P BROWN AND JOHN M SPARROW 487
Cobalt plaque versus enucleation for uveal melanoma: comparison of survival rates KIMBERLEY S ADAMS, DAVID H ABRAMSON, ROBERT M ELLSWORTH, BARRETT G HAIK, MICHAEL BEDFORD, SAMUEL PACKER, JOHANNA SEDDON, DANIEL ALBERT, AND LELA POLIVOGIANIS 494
Intravitreal injection of fibroblasts: the pathological effects on the ocular tissues of the rabbit following an intravitreal injection of autologous skin fibroblasts CATHRYN A HITCHINS AND IAN GRIERSON 498
Perforating eye injuries caused by darts M D COLE AND D SMERDON 511
The one-and-a-half syndrome Clinical correlation with a pontine lesion demonstrated by nuclear magnetic resonance imaging in a case of multiple sclerosis C N MARTYN AND D KEAN 515
Single-dose cefotaxime intramuscularly cures gonococcal ophthalmia neonatorum PHILIPPE LEPAGE, JOS BOGAERTS, PHILIPPE KESTELYN, AND ANDRÉ MEHEUS 518
Intravenous and intraocular ganciclovir for CMV retinitis in patients with AIDS or chemotherapeutic immunosuppression GEORGE L DAIKOS, JOSE PULIDO, SHASHI B KATHPALIA, AND GEORGE GEE JACKSON 521
Treatment of cytomegalovirus retinitis with ganciclovir (9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl] guanine (BW B759U)) JUAN ORELLANA, STEVEN A TEICH, JACQUELINE S WINTERKORN, USHA MATHUR-WAGH, SANDRA HANDWERGER, HARAN SCHLAMM, STEPHEN C MALAMUD, STANLEY R YANCOVITZ, DONNA M CEDERBERG, AND DONNA S MILDVAN 525

Severe herpetic keratitis. I: Prevalence of visual impairment in a clinic population CHARLES M P CLAOUÉ, MITCHEL J MÉNAGE, AND DAVID L EASTY 530

Pattern visual evoked potentials in hyperthyroidism K W MITCHELL, C M WOOD, AND J W HOWE 534

Central compaction in the process of lens growth as indicated by lamellar cataract NICHOLAS A P BROWN, JOHN M SPARROW, AND ANTHONY J BRON 538

A morphometric study of endothelial cells of human corneas stored in MK media and warmed at 37°C DAVID S ROOTMAN, SYED M HASANY, AND PRASANTA K BASU 545

Lamellar macular hole associated with idiopathic juxtafoveolar telangiectasia B PATEL, J DUVALL, AND A B TULLO 550

Acquired Brown's syndrome in a patient with combined lichen sclerosus et atrophicus and morphoea J OLVER AND P LAIDLER 552

Correspondence 558

No. 8 August 1988

Effect of single-dose invermectin therapy on human *Onchocerca volvulus* infection with onchocercal ocular involvement HENRY S NEWLAND, ALBERT T WHITE, BRUCH M GREENE, SALVATORE A D'ANNA, EZATOLLAH KEYVAN-LARIJANI, MOHAMMED A AZIZ, P NOEL WILLIAMS, AND HUGH R TAYLOR 561

Retinal burns caused by exposure to MIG-welding arcs: report of two cases G P H BRITTAIN 570

Retinoblastoma in Great Britain 1969–80: incidence, treatment, and survival B M SANDERS, G J DRAPER, AND J E KINGSTON 576

N-3-pyridylmethyl-N′-*p*-nitrophenylurea ocular toxicity in man and rabbits JOEL S MINDEL, ALEX B KHARLAMB, ALAN H FRIEDMAN, JOHN H KARAM, ROBERT D STONE, AND IRWIN M SIEGEL 584

Confidence intervals for change in automated visual fields H DUNBAR HOSKINS, SCOTT D MAGEE, MICHAEL V DRAKE, AND MARTIN N KIDD 591

Dopamine-2 receptor blockade does not affect the ocular hypotensive action of timolol QAIS A MEKKI AND PAUL TURNER 598

Long-term visual results after pars plicata lensectomy-vitrectomy for congenital cataracts STEPHEN A GROSSMAN AND GHOLAM A PEYMAN 601

A 10-year survey of penetrating eye injuries in Gwent, 1976–85 W N WYKES 607

Choroidal osteoma presenting in pregnancy B K McLEOD 612

Short-term effects of neodymium-YAG transscleral cyclocoagulation in patients with uncontrolled glaucoma O BADEEB, G E TROPE, AND C MORTIMER 615

Cavernous haemangioma presenting as an orbital mass after enucleation for a choroidal melanoma: case report A N HARNETT, P THORPE, AND J HUNGERFORD 618

Bilateral tears of the retinal pigment epithelium KAZUMI NOROSE, TSUYOSHI TANINO, AND KATSUZO SEGAWA 621

Infectious crystalline keratopathy C B JAMES, P J McDONNELL, AND M G FALCON 628

Globe luxation in histiocytosis X C M WOOD, A D J PEARSON, A W CRAFT, AND J W HOWE 631

Floppy eyelid syndrome associated with keratotorus ALEKSANDAR PARUNOVIĆ AND BOŽIDAR ILIĆ 634

α_1-Antitrypsin phenotypes in acute anterior uveitis I R FEARNLEY, D J SPALTON, A MILFORD WARD, B SLAVIN, AND F MUNCEY 636

Correspondence 640

Book review 640

Notes 640

No. 9 September 1988

Photostress recovery in chronic open angle glaucoma MARK D SHERMAN AND PAUL HENKIND 641

Birdshot chorioretinopathy: clinical characteristics and evolution HILDE A PRIEM AND JENDO A OOSTERHUIS 646

Reflow of obstructed capillaries in the maculae of humans with diabetic retinopathy, observed by fluorescein angiography YASUO YAMANA, YOSHISUKE OKA, YOSHITAKA OHNISHI, TATSURO ISHIBASHI, AND TOYOSHI INOGUCHI 660

Effects of intensified insulin treatment on retinal vessels in diabetic patients O BRINCHMANN-HANSEN, K DAHL-JØRGENSEN, K F HANSSEN, AND L SANDVIK 666

Graves' ophthalmopathy: I. Simple CT estimates of extraocular muscle volume E SVERKER HALLIN AND STEVEN E FELDON 674
Graves' ophthalmopathy: II. Correlation of clinical signs with measures derived from computed tomography E SVERKER HALLIN AND STEVEN E FELDON 678
Graves' ophthalmopathy: III. Effect of transantral orbital decompression on optic neuropathy E SVERKER HALLIN, STEVEN E FELDON, AND JEFFREY LUTTRELL 683
Pharmacokinetics of a 5-fluorouracil liposomal delivery system STEPHEN T SIMMONS, MARK B SHERWOOD, DAN A NICHOLS, ROBERT B PENNE, THEODORE SERY, AND GEORGE L SPAETH 688
Vitrectomy for idiopathic epiretinal membranes causing macular pucker SERGE DE BUSTROS, JOHN T THOMPSON, RONALD G MICHELS, THOMAS A RICE, AND BERT M GLASER 692
Corneal shape and astigmatism: with a note on myopia R A WEALE 696
Addition of hyaluronidase to lignocaine with adrenaline for retrobulbar anaesthesia in the surgery of senile cataract IAN THOMSON 700
Clinical assessment of retinal elevations: a review of methods and a novel clinical technique GEOFFREY E ROSE 703
Angiolymphoid hyperplasia with eosinophilia involving the lacrimal gland H T COOK AND N D STAFFORD 710
Unilateral proptosis as a clinical presentation in primary angiosarcoma of skull SAMRUAY SHUANGSHOTI, PRACHA CHAYAPUM, NITAYA SUWANWELA, AND CHARUS SUWANWELA 713
Book reviews 720
Note 720

No. 10 October 1988

Prevalence and causes of blindness in the Northern Transvaal PIUS J M BUCHER AND CAREL B IJSSELMUIDEN 721
Sickle cell retinopathy in Jamaican children: further observations from a cohort study J F TALBOT, A C BIRD, G H MAUDE, R W ACHESON, B J MORIARTY, AND G R SERJEANT 727
How do general practitioners manage eye disease in the community? P J McDONNELL 733
Visual recovery in orbital vasculitis A BAGEGNI, R W LYNESS, P B JOHNSTON, AND J F DOUGLAS 737
Effect of intraocular lens implantation on combined extracapsular cataract extraction with trabeculectomy: a comparative study R NEUMANN, M ZALISH, AND M OLIVER 741
The consensual ophthalmotonic reaction MARY V GIBBENS 746
Sympathetic influences on the consensual ophthalmotonic reaction MARY V GIBBENS 750
Retinal circulation during a spontaneous rise of intraocular pressure JUAN E GRUNWALD, CHARLES E RIVA, AND DAVID M KOZART 754
Stereoscopic evoked responses to crossed and uncrossed disparity accompanying simulated refractive error R A NEILL, P DUNLOP, D B DUNLOP, B FENELON, AND C DUNLOP 759
Medulloepithelioma (diktyoma) C R CANNING, A C E McCARTNEY, AND J HUNGERFORD 764
Analysis of the factors involved in cosmetic failure following excision of the eye D L SMERDON AND G A SUTTON 768
Marginal corneal abscess associated with adult chlamydial ophthalmia S DAROUGAR AND N D VISWALINGHAM 774
Optic nerve involvement in a case of methanol poisoning PETER NAESER 778
Haemangiopericytoma of the lacrimal sac a case report L CARNEVALI, F TRIMARCHI, R ROSSO, AND M STRINGA 782
Primary Ewing's sarcoma of the orbit presenting with visual loss G WOODRUFF, P THORNER, AND B SKARF 786
Ocular involvement in sinus histiocytosis with massive lymphadenopathy ZEYNEL A KARCIOGLU, BELU ALLAM, AND MICHAEL S INSLER 793
The 'poor man's' Landers lens LARRY BENJAMIN 796
Book reviews 799
Note 800

No. 11 November 1988

A rapid method of grading cataract in epidemiological studies and eye surveys V MEHRA AND D C MINASSIAN 801
A case-control study of cataract in Oxfordshire: some risk factors RUTH VAN HEYNINGEN AND JOHN J HARDING 804

Drugs, including alcohol, that act as risk factors for cataract, and possible protection against cataract by aspirin-like analgesics and cyclopenthiazide JOHN J HARDING AND RUTH VAN HEYNINGEN . . . 809
Stabilisation of refraction following cataract surgery PETER R BARANYOVITS . . . 815
Surgery of aphakic retinal detachment MOHINDER SINGH . . . 820
Visual after-effects associated with the use of high-resolution visual display units D L SMERDON AND H E WILLSHAW . . . 823
Long-term follow-up of a prospective trial of argon laser photocoagulation in the treatment of central serous retinopathy LINDA FICKER, GILLIAN VAFIDIS, ADRIAN WHILE, AND PETER LEAVER . . . 829
Changing fluorescein angiographic appearance of a subretinal membrane GIUSEPPE GIUFFRÈ . . . 835
Photocoagulation of raised new vessels by long-duration low-energy argon laser photocoagulation—a preliminary study SABAH M ZEKI AND GORDON N DUTTON . . . 837
Evaluation of a non-mydriatic camera in Indian and European diabetic patients R MOHAN, E M KOHNER, S J ALDINGTON, I NIJHAR, V MOHAN, AND H M MATHER . . . 841
Single stage insertion of the Molteno tube for glaucoma and modifications to reduce postoperative hypotony J E A HOARE NAIRNE, D SHERWOOD, J S H JACOB, AND W J C C RICH . . . 846
A case of 'low tension glaucoma' with primary empty sella SHIGEKI YAMABAYASHI, TETSUYA YAMAMOTO, TAKAYA SASAKI, AND SHIGEO TSUKAHARA . . . 852
Spontaneous reformation of upper eyelid HEMANT K MEHTA . . . 856
Blepharochalasis DONALD J BERGIN, CLINTON D McCORD, TIMOTHY BERGER, HOWARD FRIEDBERG, AND WILLIAM WATERHOUSE . . . 863
Testicular cancer presenting as a red swollen lid J A HAM AND N J CARR . . . 868
Bilateral orbital cavernous haemangiomas PETER D FRIES AND DEVRON H CHAR . . . 871
Detection and quantification of S-100 protein in ocular tissues and fluids from patients with intraocular melanoma ALISTAIR J COCHRAN, GARY N HOLLAND, ROMAINE E SAXTON, BERTIL E DAMATO, WALLACE R FOULDS, HARVEY R HERSCHMAN, ROBERT Y FOOS, BRADLEY R STRAATSMA, WILLIAM R LEE . . . 874
Correspondence . . . 879

No. 12 December 1988

Early trabeculectomy versus conventional management in primary open angle glaucoma J L JAY AND S B MURRAY . . . 881
The 12-hour control of intraocular pressure on carteolol 2% twice daily G R DUFF AND R G NEWCOMBE . . . 890
Levobunolol compared with timolol: a four-year study ORNA GEYER, MOSHE LAZAR, GARY D NOVAK, DAVID SHEN, AND CHERYL YETO . . . 892
Day-case cataract surgery M T WATTS AND J L PEARCE . . . 897
Argon laser treatment of lipid keratopathy RONALD J MARSH . . . 900
Intraocular lymphoma: immunological and cytological analysis DEVRON H CHAR, BRITT-MARIE LJUNG, JEAN DESCHÊNES, AND THEODORE R MILLER . . . 905
Primary myxoid liposarcoma of the orbit CAROL M LANE, J E WRIGHT, AND A GARNER . . . 912
Bilaterality of tears of the retinal pigment epithelium ELAINE L CHUANG AND ALAN C BIRD . . . 918
High incidence of corneal epithelium antibodies in Fuchs' heterochromic cyclitis E LA HEY, G S BAARSMA, A ROTHOVA, L BROERSMA, R VAN DER GAAG, AND A KIJLSTRA . . . 921
Predisposing factors in microbial keratitis: the significance of contact lens wear J K G DART . . . 926
Solar retinopathy following religious rituals MONIQUE HOPE-ROSS, STEPHEN TRAVERS, AND DAVID MOONEY . . . 931
Adrenaline dacryolith: detection by ultrasound examination of the nasolacrimal duct JOHN A BRADBURY, IAN G RENNIE, AND M ANDREW PARSONS . . . 935
Yersinia-induced uveitis in Ireland D F P LARKIN, M T CAFFERKEY, AND P EUSTACE . . . 938
Index . . . 942

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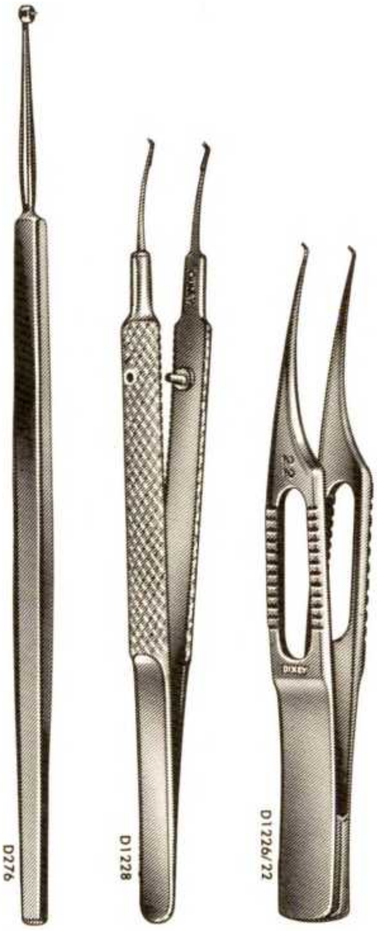

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Contents

Early trabeculectomy versus conventional management in primary open angle glaucoma J L JAY AND S B MURRAY *page* 881

The 12-hour control of intraocular pressure on carteolol 2% twice daily G R DUFF AND R G NEWCOMBE *page* 890

Levobunolol compared with timolol: a four-year study ORNA GEYER, MOSHE LAZAR, GARY D NOVAK, DAVID SHEN, AND CHERYL YETO *page* 892

Day-case cataract surgery M T WATTS AND J L PEARCE *page* 897

Argon laser treatment of lipid keratopathy RONALD J MARSH *page* 900

Intraocular lymphoma: immunological and cytological analysis DEVRON H CHAR, BRITT-MARIE LJUNG, JEAN DESCHÊNES, AND THEODORE R MILLER *page* 905

Primary myxoid liposarcoma of the orbit CAROL M LANE, J E WRIGHT, AND A GARNER *page* 912

Bilaterality of tears of the retinal pigment epithelium ELAINE L CHUANG AND ALAN C BIRD *page* 918

High incidence of corneal epithelium antibodies in Fuchs' heterochromic cyclitis E LA HEY, G S BAARSMA, A ROTHOVA, L BROERSMA, R VAN DER GAAG, AND A KIJLSTRA *page* 921

Predisposing factors in microbial keratitis: the significance of contact lens wear J K G DART *page* 926

Solar retinopathy following religious rituals MONIQUE HOPE-ROSS, STEPHEN TRAVERS, AND DAVID MOONEY *page* 931

Adrenaline dacryolith: detection by ultrasound examination of the nasolacrimal duct JOHN A BRADBURY, IAN G RENNIE, AND M ANDREW PARSONS *page* 935

Yersinia-induced uveitis in Ireland D F P LARKIN, M T CAFFERKEY, AND P EUSTACE *page* 938

Index *page* 942

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